Visueel gebied V4: Ruiscorrelaties in afwezigheid van V1 en belonings-gerelateerde activiteit.

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Visual Area V4: Noise Correlations in Absence of V1 and Reward Related Activity

Doctoral thesis

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English Summary

The use of vision to gain information about the world is a fundamental function of the brain, and is particularly important for primates like humans. While intensive research on vision has been performed during the last 70 years, we still do not understand how the detection of certain wavelengths of light is turned into the complex visual scenes filled with the discrete and recognizable objects that we perceive. Basic features of this transformation are starting to be understood, for example the detection of edges (Hubel and Wiesel 1959), but there are large gaps that remain to be filled. Visual area V4 lies on the border of our understanding of vision. While some of its basic functions are fairly clear, i.e. a role in color perception, it has other higher level features, for example extremely strong attentional modulation, the reasons for which are not understood yet (Roe et al. 2012). In this thesis visual area V4 of macaque monkeys is used to explore two factors indirectly involved in vision that have not yet been understood, noise correlations and reward. Noise correlations are signatures of neural responses that are not related to the visual stimulus that is presented, while reward signals demonstrate that the neural processing of vision is constantly being updated through learning. These factors may help us to deepen our understanding of the function of V4.

A fundamental property of brain function is that the spiking activity of cortical neurons in response to stimuli is noisy and that some of this noise is correlated between neurons, resulting in noise correlations (Gawne and Richmond 1993). This correlated activity must arise from shared input

to neurons but the neuronal circuit mechanisms that result in these noise correlations are not fully understood. This means that the reason for the existence of these correlations is still undetermined. In this thesis correlated variability in area V4 of visual cortex was recorded and examined as to whether it is altered following extensive lesions of primary visual cortex (V1). To this end we recorded from tens of electrodes in visual area V4 of two behaving macaque monkeys while they fixated a gray screen and then calculated noise correlations. These recordings were made using a Utah array and were longitudinal. Roughly 2 weeks after the start of the recordings an extensive V1 lesion was performed and I examined what happened to noise correlations on the same pairs of electrodes both before and after the lesion.

If noise correlations were the result of a cascade of shared feedforward input then this manipulation would be expected to decrease the noise correlations. However, if noise correlations were mostly generated by firing fluctuations in the local circuit or shared feedback input from higher order areas then we would instead see an increase or maintenance of noise correlations, which is what was observed. I found that the correlations of neuronal activity survived the lesions in both monkeys. In one monkey, the correlation of multi-unit spiking signals was strongly increased in the first week post-lesion, this was despite the fact that MUA stimulus responses decreased (Schmid, Schmiedt, et al. 2013). In the second monkey, correlated activity was also increased but only slightly, and this increase was not greater than some week-by-week fluctuations observed. The typical drop-off of noise correlations with cortical distance was preserved after the lesion (Smith and Kohn 2008). In one monkey spike train correlation values also demonstrated an increase post lesion despite the very different time scale of this measure. Therefore, as V4 noise correlations remain without feedforward input from V1, these results suggest instead that local and/or feedback input seem to be necessary for correlated activity, addressed on multiple different timescales and on different spatial scales.

I additionally investigated reward related neural activity in area V4. Reward related activity has been intensively studied in high-level areas such as LIP and FEF in the visual system. However, recent evidence has indicated that early visual areas also show reward related activity (Arsenault et al. 2013; Baruni, Lau, and Salzman 2015). As reward biases the decision criteria of subjects performing discrimination tasks, I investigated how reward affected the neural activity in the visual cortex during a discrimination task. I recorded neuronal activity in area V4 using implanted Utah arrays

in two macaques previously trained on a motion discrimination task. This task was modified to include reward information, on each trial a colored reward cue informing the subject of the reward value of each motion direction. However, only when the correct motion direction was chosen would the reward be given. When the reward amounts were uneven, macaques were biased towards choosing the option with higher reward, as has been reported previously (Rorie et al. 2010).

I hypothesized that area V4 would enhance the representation of the rewarded motion direction by increasing firing rates during the high reward conditions similarly to previous attention studies (Maunsell and Treue 2006). However, unexpectedly, during the time period immediately after the reward cue onset, what I found was a suppression of the response to the stimulus within the receptive field. The size of this suppression was dependent on both the amount of reward signaled by the cue and the distance of the cue from the receptive fields of the neurons. Surround suppression is thought to allow the brain to efficiently represent stimuli and can be enhanced with attention to a stimulus. However, the novel finding that the amount of reward predicted scales the amount of suppression may point to a role for V4 is representing factors other than visual information.

By investigating changes in V4 activity with noise correlations and reward this thesis explores how internal factors can effect brain activity. This is in contrast to most studies which are engaged in how external factors affect neural activity in sensory areas. Studying internal factors is very important as many lines of evidence point to the fact that our perception of the world around us is not based on what is physically present, but instead what is expected to be present or has been learned or remembered. Investigating these internal factors will hopefully lead us to understand how the brain makes these highly complex inferences.

Dutch Summary

Het gebruik van visuele informatie om de wereld om ons heen te begrijpen is een fundamentele eigenschap van het brein en is in het bijzonder belangrijk voor primaten, waartoe ook mensen behoren. Ondanks het diepgaande onderzoek dat de afgelopen 70 jaar heeft plaatsgevonden naar het functioneren van het gezichtsvermogen, begrijpen we nog steeds niet hoe het detecteren van bepaalde golflengtes van licht wordt omgezet in het waarnemen van complexe visuele taferelen vol met afzonderlijke en herkenbare objecten. Basale kenmerken van deze transformatie worden steeds beter begrepen, bijvoorbeeld het detecteren van randen (Hubel en Wiesel 1959), maar er zijn nog steeds grote hiaten in onze kennis. Het visuele gebied V4 ligt aan de grens van ons begrip van het gezichtsvermogen. Hoewel sommige basale functies van V4 redelijk duidelijk zijn, zoals bijvoorbeeld zijn rol in kleurwaarneming, heeft het ook eigenschappen die op hogere functies duiden, zoals bijvoorbeeld een erg sterke modulatie door aandacht, waarvan de redenen nog niet duidelijk zijn (Anna W. Roe et. al 2012). In dit proefschrift wordt visueel gebied V4 van makaken gebruikt om twee factoren te onderzoeken die indirect bijdragen aan ons vermogen om te zien en die nog niet begrepen worden: ruiscorrelaties en beloning. Ruiscorrelaties zijn signalen die getuigen van neuronale responsen die niet gerelateerd zijn aan de gepresenteerde stimulus. Beloningssignalen demonstreren dat het verwerken van visuele stimuli continue wordt bijgestuurd door leren. Deze factoren zouden ons erbij kunnen helpen de functie van V4 beter te begrijpen.

Een fundamentele eigenschap van het brein is dat de spike-activiteit (ac-

tiepotentialen) van corticale neuronen als reactie op stimuli ruis bevat. Een deel van deze ruis is gecorreleerd tussen neuronen, wat leidt tot ruiscorrelaties (Gawne and Richmind 1993). Deze gecorreleerde activiteit ontstaat uit gedeelde invoer aan neuronen, maar de neuronale netwerkmechanismen die leiden tot ruiscorrelaties zijn niet volledig bekend. Dit heeft tot gevolg dat de reden voor het bestaan van ruiscorrelaties nog onduidelijk is. Voor dit proefschrift werd de gecorreleerde variabiliteit in visueel gebied V4 opgetekend en er werd onderzocht of deze veranderde nadat grote delen van de primaire visuele cortex (V1) waren verwijderd. Met behulp van tientallen electroden in visueel gebied V4 werden bij twee wakkere, alerte makaken metingen verricht terwijl die hun blik op een grijs scherm fixeerden; hiermee werden de ruiscorrelaties berekend. Deze metingen werden verricht met een "Utah array" en waren dus longitudinaal. Ongeveer twee weken nadat de metingen waren gestart werd een uitgebreide laesie aangebracht in V1 waarna ik onderzocht wat er gebeurde met de ruiscorrelaties tussen dezelfde electrodenparen voor en na de leasie.

Indien ruiscorrelaties het resultaat zijn van een cascade aan gemeenschappelijke "feedforward-invoer", is de verwachting dat deze manipulatie de ruiscorrelaties zal verminderen. Echter, indien ruiscorrelaties het resultaat zijn van fluctuaties in de activiteit van het lokale netwerk of van gemeenschappelijke "feedback-invoer" van gebieden op een hoger niveau in de hiërarchie, is de verwachting dat we juist een behoud of toename zullen zien van ruiscorrelaties. Dat laatste is wat we observeerden. Ik vond dat de correlaties van neuronale activiteit in beide apen gehandhaafd bleven na de laesies. In de eerste week na het plaatsen van de laesie waren in één van apen de correlaties tussen de multi-unit signalen sterk toegenomen, ondanks dat de MUA responsen op de stimulus afnamen (Schmid, Schmiedt et al. 2013). In de tweede aap was de gecorreleerde activiteit ook toegenomen, maar deze toename was niet groter dan de wekelijkse variatie. De typische afname van ruiscorrelaties met het vergroten van de afstand tussen de corticale meetpunten bleef behouden na de laesie (Smith en Kohn 2008). In één aap waren de waardes van SUA correlaties ook verhoogd na de laesie, ondanks dat deze maat een complete andere tijdspanne heeft. Met verscheidene temporale en ruimtelijke schalen stellen we dus vast dat ruiscorrelaties in V4 ook gehandhaafd blijven zonder "feedforward-invoer" vanuit V1, wat erop duidt dat er lokale en/of "feedback-invoer" nodig is voor gecorreleerde activiteit.

Tevens heb ik de belonings-gerelateerde neuronale signalen in hersengebied V4 onderzocht. Belonings-gerelateerde signalen zijn al uitgebreid onder-

zocht in hersengebieden op een hoger niveau in de hiërarchie, zoals LIP en FEF in het visuele systeem. Recente bewijzen lijken er echter op te duiden dat visuele gebieden op een lager niveau ook belonings-gerelateerde signalen vertonen (Arsenault et al., 2013; Baruni, Lau, en Salzman 2015). Aangezien beloning de besluitvormingscriteria van proefpersonen beïnvloedt in taken die het onderscheidingsvermogen testen (discriminatie taken), onderzocht ik hoe beloning de neuronale activiteit in de visuele cortex beïnvloedde tijdens een discriminatie taak. Ik verrichte metingen in visueel gebied V4 met geïmplanteerde "Utah arrays" in twee makaken die voorheen al getrained waren op een discriminatietaak. Deze taak werd aangepast om beloningsinformatie mee te laten wegen: tijdens iedere proef was er een gekleurd teken dat aangaf hoeveel waarde iedere bewegingsrichting had. Alleen indien de juiste bewegingsrichting werd gekozen, werd de aap daadwerkelijk beloond. Indien de beloningswaardes niet gelijkwaardig waren, neigden de makaken ertoe om de optie met de hogere beloning te kiezen, zoals voorheen ook beschreven is (Rorie et al. 2010).

Mijn hypothese was dat visueel gebied V4 de representatie van de beloonde bewegingsrichting zou versterken door het actiepotentialentempo tijdens de toestand met de hoge beloning te verhogen, vergelijkbaar met eerdere studies naar aandacht (Maunsell en Treue 2006). Ik ontdekte echter onverwachts, dat in de tijdsperiode direct na de presentatie van het beloningsteken, er juist een afname was van de respons op de stimulus in het receptieve veld. De omvang van de afname was zowel afhankelijk van de hoeveelheid beloning die het teken signaleerde als van de afstand van het teken tot de receptieve velden van de neuronen. "Omgevingsonderdrukking" wordt gezien als een manier van het brein om stimuli efficiënt weer te geven en het kan versterkt worden door aandacht. De nieuwe bevinding is echter dat de door het teken voorspelde hoeveelheid beloning, de omvang van de onderdrukking schaalt. Dit kan erop wijzen dat V4 een rol speelt bij het weergeven van andere factoren dan alleen visuele informatie.

Dit proefschrift verkent hoe interne factoren hersenactiviteit kunnen beïnvloeden door onderzoek te doen naar de veranderingen in V4-activiteit door ruiscorrelaties en beloning. Dit staat in tegensteling tot de meerderheid van de onderzoeken die zich bezighouden met hoe externe factoren neuronale activiteit in sensorische gebieden beïnvloeden. Het bestuderen van interne invloeden is erg belangrijk. Meerdere bewijzen tonen namelijk aan, dat hoe wij de wereld om ons heen waarnemen niet gebaseerd is op wat fysiek aanwezig is, maar op wat wij verwachten dat aanwezig is of wat we aangeleerd hebben of wat we ons herinneren. Het onderzoeken van deze

interne factoren zal er hopelijk toe leiden dat we kunnen begrijpen hoe het brein deze zeer complexe gevolgtrekkingen maakt.

Chapter 1

Introduction

1.1 General introduction

Neuroscience is the study of the nervous system of animals. However, the nervous system is unlike any other organ in the body. Not only does the nervous system ensure that all the organs of the body communicate and work together, and allow coordinated actions like movement, but it also controls the behavioral states of the organism, which in humans includes feelings ranging from thirst all the way to intellectual curiosity. Scientists only really started the monumental task of researching into a complex system like this during the last 100 years. Evidence for the generation of action potentials, the fundamental unit of communication between neurons within the nervous system, was only discovered in 1939 (Hodgkin and Huxley 1939). Although many other important discoveries have since been made, neuroscientists are still at the beginning of the journey of understanding how the nervous system functions.

Understanding sensory systems of organisms is necessary to work out how the brain encodes information about the outside world. Due to the precise control over stimuli and the behavioral importance of sight, particularly in humans, the visual system has been a heavily studied part of the nervous system. The fact that it is so well studied was an important factor in in-

vestigating the visual system further in this thesis; because of the thorough understanding of basic functions I was able to start asking more complex functional questions. Most studies look at perception as a unidirectional process, i.e. that sight comes into the eye and is processed step by step through the system, However, recently it has become clear that internal processes, for example expectations of what types of objects are in the nearby environment, can have effects on very early stages of perception. Area V4 in the visual system of primates is a fairly early sensory area but one which has been shown to have very strong modulation of activity by extra-retinal factors. This makes it a highly interesting area to investigate.

This work highlights two little explored aspects of area V4 in the primate cortex, namely, how do noise correlations arise in area V4 and how does V4 activity change under varying reward conditions. In chapter 1, Introduction, I will introduce generally the subjects involved in this work. Section 1.1 will introduce the visual system as a whole, then talk about what's special about the primate visual system and finally explain in more detail what is area V4, what are noise correlations (section 1.2) and what is reward related activity (section 1.3). In chapter 2, Noise Correlations, I will detail how I investigated noise correlations in area V4 in data where area V1 was lesioned, what results I found and discuss implications of these findings. In chapter 3, Reward Related Activity, I will detail the experiments I did to record multi-unit activity in area V4 under different reward conditions, what I found and what the implications of these findings are. In the final chapter, chapter 4, Conclusion, I will summarize the implications of the noise correlation and reward results I have for V4 and the brain.

The visual system

At its most basic level, vision is the ability of neurons to detect some wavelengths of light. The sun, moon and stars all provide a wide range of wavelengths of light which are absorbed and reflected to different extents by different types of material. Being able to detect how much light is present in the environment is already highly informative because natural light almost always comes from the sky. This can already give organisms a direction so that they are not just moving around in circles (you can see this in moths flying into candles, they are responding as if it were the moon). With more specialized anatomy around these light detecting neurons an eye is formed. It is thought that the eye has evolved independently 50-100 times from primitive photosensitive cells, but it has often ended up with similar features (see Figure 1.1). These are a cup shaped layer of light responsive

neurons (the retina) to give directionality of light, a lens (or lenses) to focus the light onto these light responsive neurons and placement in the general direction of motion of the animal (Gehring 2005). The fact that it has evolved independently so many times shows how useful vision is to survival, it is worth the costs of the complicated anatomy necessary to support it. It is the only sense through which you can passively gather information about objects, and their distance in relation to both you and to each other. According to one theory, the eye may have actually evolved before the brain and that the brain evolved to process all the information that vision supplies (Gehring and Ikeo 1999), as there are, for example, unicellular algae that can respond to light directly by changing the direction of their motion (Witman 1993).

In mammals there are two main types of photosensitive cells in the retina, rods and cones, which are named after their slightly different shapes (Kandel, James, and Jessell 2000). Both respond to light by changes in the cell membrane potential (hyperpolarization) through a process called phototransduction. Cones are specialized for color vision and have different subtypes that are responsive to different wavelengths of light. They need to be exposed to a large number of photons to be able to respond with changes in membrane potential. Rods, on the other hand, are far more sensitive, they can detect single photons, and dark-adapted humans are able to consciously perceive only 5-14 photons hitting their retina (Hecht, Shaler, and Pirenne 1941), which is equivalent to being able to see a single candle 30 miles away. However, rods are much slower to respond than cones as they need to summate the photons over time. Rods are responsible for vision during low light conditions and cones are responsible for high acuity vision (sharp images) of fast moving objects in good light conditions. The signals from these cells are transmitted to bipolar cells and then ganglion cells before being sent into the first stage of visual processing in the brain, the lateral geniculate nucleus (LGN) in the thalamus. In the LGN the signal from both eyes has not yet been combined but cells start to respond specifically to features like color and motion. How exactly the signals from these two different types of photoreceptor are combined in the brain is an active area of research. From there the visual information enters the cortex mainly through primary visual cortex area V1, although there are projections to other cortical areas as well as directly to motor areas like the superior colliculus (SC). In mammals a large portion of the brain and in particular the cortex is devoted to processing visual information.

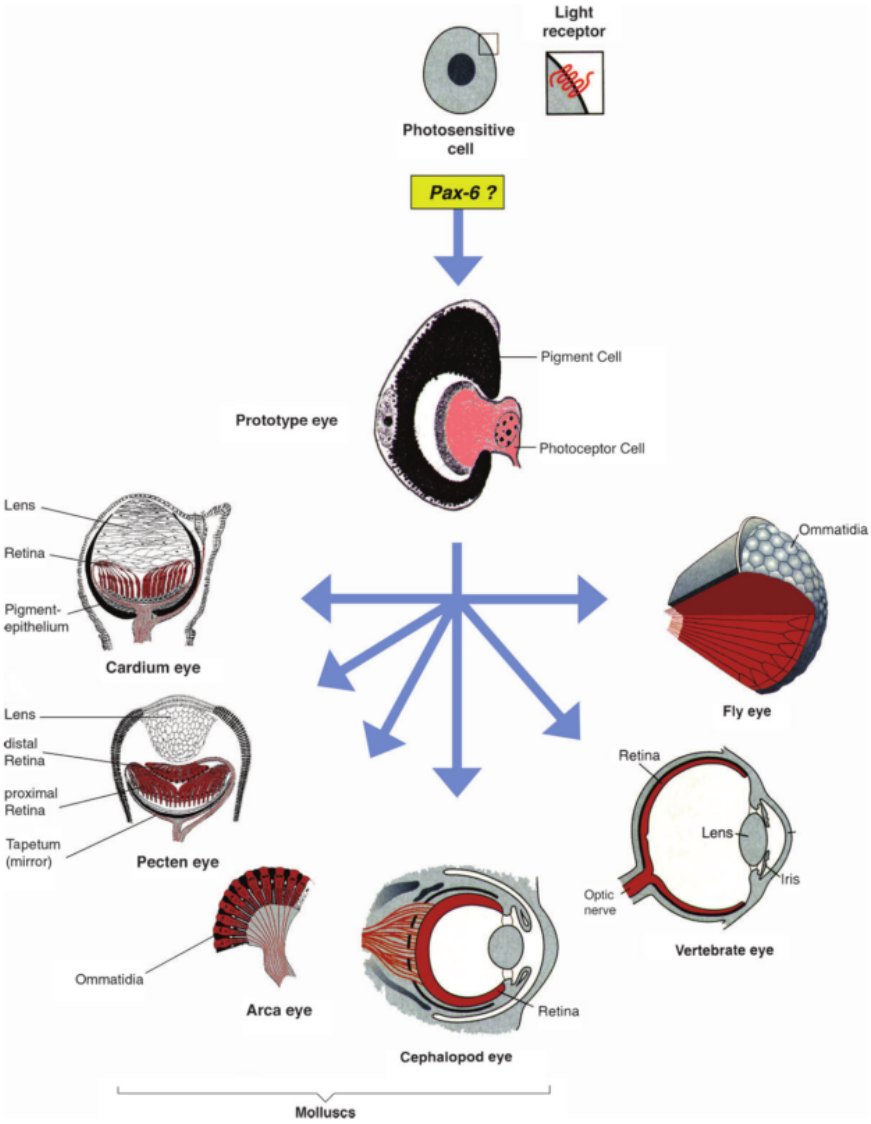

Figure 1.1 | The eye has evolved multiple times from primitive photosensitive cells. Taken from Gehring (2005) Figure 8.

Primate vision

As explained in the previous section vision is an extremely important sense. However, for primates vision has become the primary mode of interaction with the outside world. Particularly noticeable in humans is that the acuity of hearing and smell is far worse than other diurnal omnivores (e.g. dogs and bears) but the acuity of vision surpasses any other mammal. Most primates have many specializations including a richly populated fovea of only cones, each projecting to a single bipolar cell for high acuity color vision in the center of gaze (primates have a far higher density of cones than any other mammalian species (Wässle 2004)) and highly overlapping binocular vision for excellent depth perception. There are several theories about why this is, but one is that a red responsive cone cell re-evolved in primates due to the importance of fruit in the diets of early primates, red/green discrimination is very important for discerning different types of fruit among foliage (Regan et al. 2001). In macaques almost half of the area of the entire cortex is predominately used to represent vision, only one of the five senses (Van Essen 2004). Perhaps due to this high acuity sight, vision has become a vital tool for communication in primates. Primates are the only animals known to have "covert attention", the ability to aim their center of gaze at one object but pay more attention to another object. This is likely so that they can observe the actions of their conspecifics without communicating a challenge or another interaction.

One of the classic papers in the field of visual neuroscience is Felleman and Van Essen (1991). They arranged the visual areas of macaque monkeys in a hierarchy based on anatomical connections between them. They argued that vision is processed serially throughout this hierarchy becoming more and more complex until reaching the visual association areas. This view was prevalent for the next 20 years and it is only recently that the role of feedback projections (projections from higher areas to lower areas in the hierarchy) in driving visual processing have been seriously investigated. The surge of interest in these feedback projections is due at least in part to Gestalt psychologists, who have argued for many years that our perception of the world is based heavily on what we expect to be present rather than what is actually there. For example we have no problem perceiving objects that are partially blocked by other objects, despite this making a large difference to the image that lands on the retina. Recently it has been found that even in primary visual cortex there are responses to "illusory contours", lines that are not present but is only suggested due to occlusion. Observations like these and the presence of numerous other optical illusions

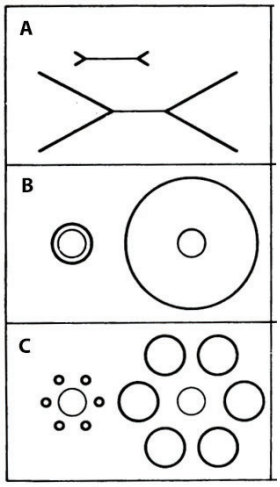

Figure 1.2 | Size illusions likely caused by global object integration operating through feedback projections. In A this is due to the size of the proximal elements, in B due to the spacing between elements and in C due to the spacing and size of elements. Adapted from Day (1972) Figure 2.

suggest that feedback from higher areas has a much stronger effect on perception than was initially realized (Figure 1.2). This has called for a new view of visual processing that, at least in primates, expectations of visual input must shape perception, but exactly how this might take place has not yet been well understood.

In primate vision, which has been heavily studied in macaques, after visual information enters the cortex via the primary visual cortex it is split into two streams, see Figure 1.3. These two streams are thought to be related to the magno and parvo cellular split in the retina and LGN. Magno cells respond mostly to low spatial frequency, fast moving stimuli while parvo cells respond to high spatial frequency stimuli at lower speeds. The magno cells input to the dorsal stream, which goes from V1 to areas MT and LIP and is thought to be specialized for visual movement information and results in action. The parvo cellular input to the ventral stream goes from V1 to areas V4 and IT and is thought to be specialized for object recognition. Lesions to these pathways cause very different types of visual deficits, with ventral stream lesions causing various types of agnosia and inabilities to learn new objects while dorsal stream lesions cause deficits in visually guided movements, for example tracking eye movements or visually guided reaching (Desimone, Schein, et al. 1985; Newsome, Wurtz,

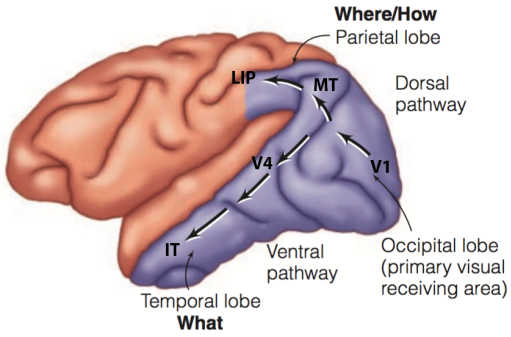

Figure 1.3 | Dorsal and ventral stream shown on a macaque brain. Adapted from Goldstein (2009) Figure 4.27.

et al. 1985). Area V4, the subject of this thesis, is part of the ventral stream and receives most of its feedforward and feedback input from other areas within the ventral stream. All of the early areas in the ventral stream respond well to edges and contours but in area IT, one level above V4 in the cortical hierarchy, neurons become selective to particular objects. IT neurons have an average receptive field (RF) size of 25° (Desimone, Schein, et al. 1985) but are sensitive to the same objects placed anywhere within this area. Eventually this stream involves areas like FFA and PPA which have cells selective for faces and objects respectively and are invariant to the rotation of the objects they are selective for. In these higher areas the percept of objects cannot be elicited by stimulation but can be interfered with (Rangarajan et al. 2014).

While macaque monkeys have the most heavily studied brains of primates, much work has been done that shows that the principles that are true for macaque monkeys also apply to other primates and in particular humans. Functional magnetic resonance imaging (fMRI), which uses the oxygen level of blood to localize brain activity, has been done in both humans and macaques and using this data homologues of most of the visual cortical areas found in macaques have been identified in humans (Orban, Van Essen, and Vanduffel 2004). These cortical areas are also arranged in a similar pattern on the human cortex as in the macaque. While a homologue of area V4 is slightly more contentious, there is evidence that it does exist in humans. Therefore it is likely that the work done on area V4 in macaques within this thesis is valid for humans as well as for macaques. This is important for any future work that builds on this research, for example there

is currently intensive research into prostheses for blind people (Wyk et al. 2015) which would benefit from a detailed knowledge of the computations performed by every visual area of the cortex.

Area V1

Area V1, also called primary visual cortex or the striate visual cortex, due to the distinctive striation of the line of Gennari, is a well understood brain region which is the entry point of visual information to the cortex. This is the largest visual cortical area and almost all axons from LGN project to V1 (Sincich et al. 2004). It is the first stage of the visual hierarchy that combines information from the left and right eye, using optical dominance columns, in order to make the uninterrupted visual scene that we perceive. Neurons within area V1 mostly are tuned to basic features of small areas (around 0.5-3 visual degrees) of visual stimuli, for example contrast and orientation (Hubel and Wiesel 1974; Hubel and Wiesel 1959). The exact area that a neuron responds to is called its receptive field (RF), explained in more detail in Figure 1.4. Due to its easily accessible location on the surface of the back of the brain this was one of the earliest investigated cortical brain regions (Hubel and Wiesel 1959; Hubel and Wiesel 1962) and one of the earliest papers to use the concept of cells having a RF.

While V1 neurons mostly respond to basic properties of stimuli there is some evidence that even V1 neurons can be influenced by extra-retinal processes, for example attention (Roelfsema, Lamme, and Spekreijse 1998) or prior expectations (Berkes et al. 2011; Kok, Jehee, and Lange 2012). This likely takes place through feedback influences from higher cortical areas including V4 (Lamme and Roelfsema 2000). Although not fully understood, the role of these feedback projections are thought to be vital for our ability to bind together objects and perceive them as coherent wholes (Romei et al. 2011). Feedback projects are also thought to be important for the development of the so called “extraclassical receptive field”, mostly apparent as surround suppression. The classical RF of a V1 neuron is the area of visual space that the neuron increases its firing to with a small stimulus. However, if a stimulus larger than the RF center is placed over the RF, in most cases something called surround suppression takes place. This means that making the stimulus larger actually decreases the firing rate of the neuron (see Figure 1.4). A similar decrease in firing can be seen by adding a second small stimulus into the area just outside the classical RF. The extent of the area in which you can add a second stimulus and change the response of the neuron to the stimulus in the classical RF is the

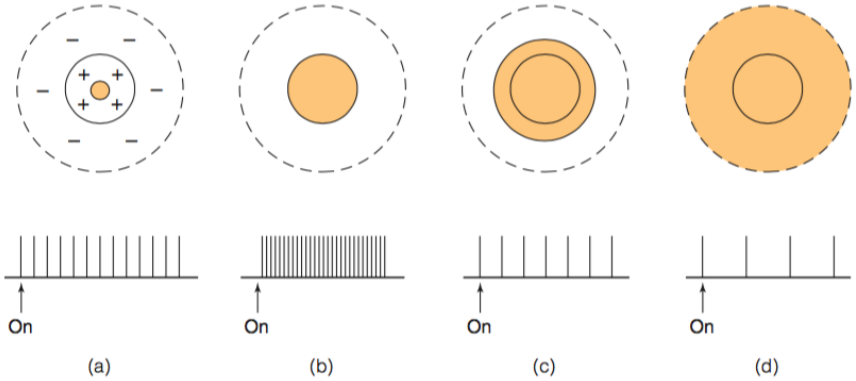

Figure 1.4 | Image of how a visual RF works. The first row is a schematic of the responses of visual area of the RF. The second row are idealized spiking responses of a neuron with the shown RF from the placed stimulus (orange circle). Minuses are the suppressive surround while pluses are the excitatory center of the RF. In (a) the stimulus is too small to fully excite the neuron. In (b) the stimulus is exactly the right size to get the maximum response. In (c) and (d) the more of the suppressive surround that the stimulus takes up the more the firing of the neurons is reduced. Taken from Goldstein (2009) Figure 2.19

extraclassical RF.

Area V1 is vital not only for the representation of small features of the visual scene, but seemingly also for our ability to consciously perceive visual stimuli. In humans when area V1 is badly damaged patients display symptoms called blindsight or cortical blindness. In this phenomena patients claim that they are completely blind, i.e. consciously they are not able to see anything. However, when tested carefully it seems that subconsciously they are still able to detect things in the area in which they say they are "blind" (Stoerig and Cowey 1997). For example, they are able to avoid or even catch objects that are thrown towards them (Midorikawa et al. 2008), although they continue to claim that they cannot see them. They are even able to do more complicated tasks like guessing the identity of an object, although again they claim that they cannot see it. In humans area V1 damage is usually due to stroke and the extent of the damage is not constrained and cannot always be fully identified. However, as macaque monkeys which, as explained in the previous section, have a very similar area V1 we can make precise lesions and investigate what happens. By lesioning V1 of macaque monkeys, as in chapter 2, the majority of the feedforward input to the rest of the visual cortical areas is removed. While

it is unknown exactly how this takes place, there are studies suggesting that pathways that do not project via V1 are preserved and that this residual visual information is able to be processed through the rest of the visual system (Schmid, Mrowka, et al. 2010; Schmid, Schmiedt, et al. 2013; Lamme 2001). While there is reduced but significant activity in response to visual stimuli in V4 after V1 lesion, the nature of this activity shows that the lesion causes fundamental changes to the response properties of the neurons. Despite this research it is still unknown why blindsight patients do not have conscious access to this alternative visual information.

Area V4

In this thesis the focus is area V4, a midlevel area in the visual cortical hierarchy. V4 is an area found in primates spread between a dorsal and ventral section which represent different sections of the visual field. In both chapters 2 and 3 we have recorded from the dorsal section of V4 through Utah arrays implanted on the surface of the cortex. V4 receives a small part of its feedforward input from V1, but most from areas V2 and V3 (Ungerleider et al. 2008). V4 provides retinotopically based feedback to all early visual cortical areas and feedforward input to area TE and TEO in the ventral stream (Ungerleider et al. 2008). As it is already some stages into the visual hierarchy V4 neurons have complex response properties and RFs ranging from 4 to 6 times larger than V1 RFs at similar eccentricities (Desimone, Schein, et al. 1985). V4 was initially identified as a color area based on the large proportion of cells responding to color and that they are clustered by columns (Zeki 1973) (see Figure 1.5). However, more recently studies have shown that V1 and V2 also contain many color selective cells, and most cells in V4 are not finely tuned to particular wavelengths (Desimone, Schein, et al. 1985) therefore the role of V4 in color is not as clear as it initially seemed. It is clear though that V4 is heavily involved in our perception of color constancy, i.e. that we can perceive objects as being made up of one color despite differences in the amount of light hitting them due to shadows etc (Desimone, Schein, et al. 1985; Kusunoki, Moutoussis, and Zeki 2006; Vaina 1994). In addition, in humans it has been shown that microstimulation of V4 causes a color percept (Murphey, Yoshor, and Beauchamp 2008). V4 also contains neurons that are highly selective for shape. While it is currently unknown what the exact role of V4 is it seems likely that it contains neurons that reflect features of objects. For example some V4 neurons are selective for curves (complex edges) and surface colors. They are also very sensitive to stimuli in their surround meaning that they may be vital for figure-ground separation (Roe et al. 2012). After V4

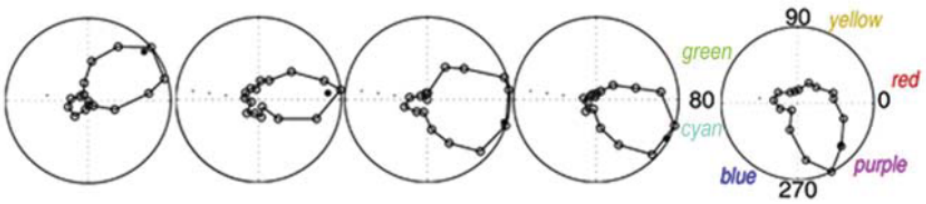

Figure 1.5 | V4 neurons are tuned to color. Recordings from 5 neurons on a single electrode track shows that as an electrode down through V4 neurons gradually shift their color tuning (in this case from orange to red through to purple). Taken from Roe et al. (2012) Figure 2.

lesions there are a diverse range of impairments including 2D and 3D shape recognition as well as color constancy (Walsh et al. 1993) and an inability to select stimuli that are not relevant (De Weerd et al. 1999; Schiller 1993). These studies point to a possible role for V4 in separating objects from backgrounds.

Most research on area V4 has been to investigate the effects of attention on neuronal firing. A search in PubMed for the words V4 and attention in the title and abstract returns more than 250 papers (as of 09/02/17). While in area V1 effects of attention are present but minimal (Motter 1993), in area V4 attention can change the average firing of neurons by more than half (Moran and Desimone 1985), see Figure 1.6 for an example neuron. If there are two stimuli in the RF of a V4 neuron with the attended stimulus non-preferred and unattended stimulus preferred, the firing pattern can look as though only the non-preferred stimulus is present (Reynolds, Chelazzi, and Desimone 1999). Even stronger signals of attentional modulation are found if changes in the indices of gamma power or noise correlations are examined rather than raw firing rate (Cohen and Maunsell 2009). The attraction for studying area V4 in regards to attention seems to be that it is easily accessible and has RFs that can be simply characterized while still showing attention effects. However, the reason that V4 shows such strong attention modulation is unknown. But, as suggested above, if V4 is involved in the perception of foreground and background then it would make sense for it to be highly selective for relevant vs irrelevant stimuli.

1.2 Noise correlations

Successfully perceiving a brief visual stimulus entails being able to use a single presentation to characterize its properties. Despite this, we know

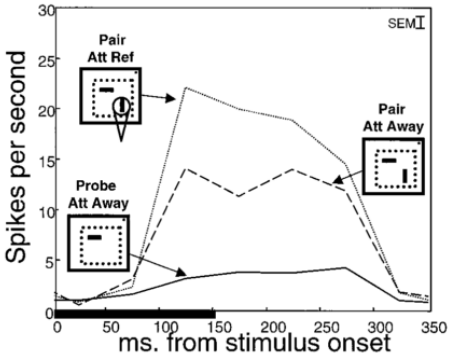

Figure 1.6 | V4 neurons respond very differently depending on which stimulus they need to attend to, despite the stimulus being unchanged. Taken from Reynolds, Chelazzi, and Desimone (1999) Figure 7.

that repeated presentations are needed to characterize a cortical neuron's response to a stimulus, due to "noise" in the neural responses. In this view the portion of the response of the neuron that is due to the stimulus would be "signal" and anything besides that is viewed as "noise". The use of quotes here is to indicate that this may not necessarily be the case and there could be useful information in the "noise" portion of the response, but it is the component not directly due to the outside stimulus. This "noise" or variability in responses has been shown to be large (Schölvinck et al. 2015; Shadlen and Newsome 1998) and is the reason why many papers reporting neuronal activity show peri stimulus time histogram (PSTH)s, which are the pooled responses to a stimulus over trials, instead of single trial activity.

Importantly, it has been shown that a small amount of this "noise" is shared among neurons (Cohen and Kohn 2011; Zohary, Shadlen, and Newsome 1994; Gawne and Richmond 1993), this is termed noise correlation. Noise correlations are often also described as "correlated variability", as it is the variability around the mean response on each trial which is, to a small extent, correlated between neurons (Cohen and Kohn 2011). This "noise" in the responses of neurons is interesting because it makes it impossible to ascertain on single trials from a single neuron what stimulus has been shown but the brain is obviously somehow able to solve this task. If the variability were independent between neurons it would be fairly easy to remove on single trials by merely averaging over the responses of multiple neurons. As soon as components of the "noise" are correlated, averaging

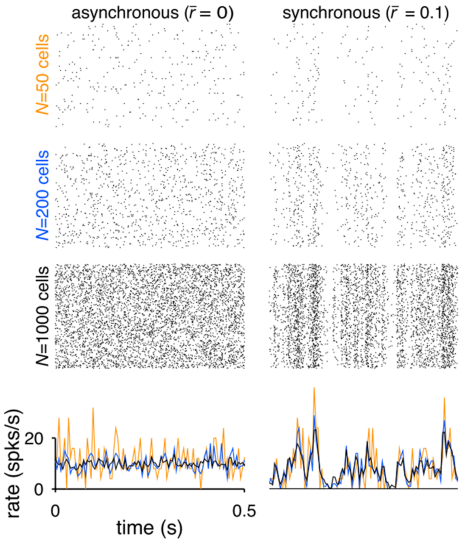

Figure 1.7 | While correlation values of 0.1 do not sound impressive they can make a large difference to activity when pooled over multiple neurons. Taken from Renart et al. (2010) Figure S2.

across multiple neurons is no longer an effective way to reconstruct the true stimulus (see Figure 1.7).

Much research has been done to investigate the levels of noise correlations found in the brain (for review see Cohen and Kohn (2011)). While there is some debate, the general agreement seems to be that neurons have a small but positive noise correlation with one another. The magnitude of the observed correlation varies depending on the firing rate of the neurons that are being recorded from, this is thought to be due to low firing rates disguising the correlated membrane potential fluctuations happening within the neurons. However, the magnitude can also vary with brain state, cortical area and flexibly with task behavior (Cohen and Maunsell 2009; Cohen and Kohn 2011; Renart et al. 2010; Deweese and Zador 2004). Noise correlations may also be different depending on what stimuli are presented. This may be a signature of their origin which will be discussed in more detail below.

Theoretical implications of noise correlations

Noise correlations are important for understanding how the brain can optimally read out incoming signals. With a large population of neurons,

pooled responses from all of them can theoretically be used to reconstruct the stimulus. However, this works best if the "noise" is uncorrelated (or anti-correlated) between neurons that have similar tuning curves (Averbeck, Latham, and Pouget 2006; Panzeri et al. 1999; Zohary, Shadlen, and Newsome 1994). It has been shown that even small shared correlations can have a large effect on the readout of this activity (see Figure 1.7) and may explain why the limits of our abilities to detect stimuli are so close to the limits of single neurons (Cohen and Maunsell 2009; Zohary, Shadlen, and Newsome 1994). To examine this issue in more detail many theoretical studies have been performed. From these studies it seems that the type of task being performed changes whether noise correlations are harmful or beneficial. They are also stimulus dependent (Kohn and Smith 2005).

There are two main types of noise correlations that have been examined. The first is rate correlation (or spike count correlation), which is the most common. In this measure spike counts are summed over long windows, commonly at least 500 ms, and then this value is correlated between two neurons over trials. This means that the correlations are present at time scales of larger than 500 ms and exist for the duration of several hours of recording from the neurons. A second type is called spike train correlations. In this measure it is attempted to directly correlate the spike trains of two neurons on a very fast timescale of around 10 ms. The values seen using this measure tend to be far lower than those using rate correlations but are still positive on average (Renart et al. 2010). These two types also have different theoretical implications depending on whether or not spike timing is taken to be an important measure of brain activity.

How do noise correlations arise?

When an individual neuron is examined in a dish responses are not variable at all, injecting a certain level of current will result in a certain number of spikes highly reliably. Levels of "noise" in responses to a stimulus are low in subcortical early visual areas (the retina and LGN) and increase in the cortical higher areas (Schölvinck et al. 2015; Shadlen and Newsome 1998; Churchland et al. 2010; Kara, Reinagel, and Reid 2000). However, the question remains, where do these correlations come from? Despite the theoretical importance of noise correlations this question has not yet been answered. A classic view of correlated activity emphasizes the potential role of shared feedforward input (Ecker, Berens, Keliris, et al. 2010; Gawne and Richmond 1993; Shadlen and Newsome 1998) but studies demonstrating beneficial changes in noise correlations as a function of higher order

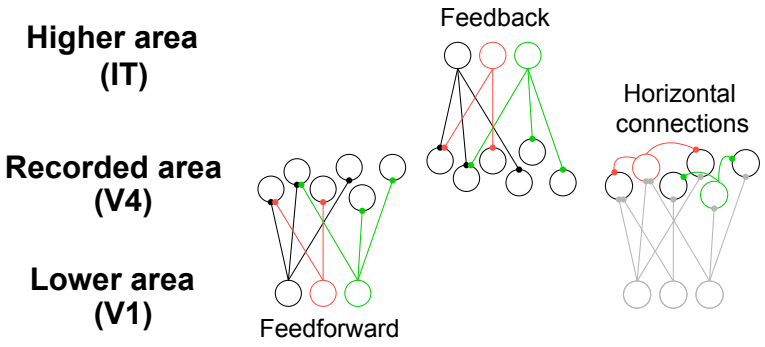

Figure 1.8 | There are multiple possible mechanisms through which shared variability could arise. Here is an illustration of how shared connections between neurons could cause correlated variability.

processes like attention or perceptual learning (Cohen and Maunsell 2009; Gu et al. 2011; Ruff and Cohen 2014) point to a potential origin from higher visual areas. Alternately, noise correlations may be a product of the local inhibitory circuit as even highly correlated input can be desycnchronised by local interneurons (Renart et al. 2010). This is also suggested by the spatial structure of noise correlations which decrease monotonically with the distance between the neurons in the pair (Smith and Kohn 2008; Smith and Sommer 2013). Correlated neuronal variability could arise from multiple possible brain circuit mechanisms, including common feedforward projections from lower areas, feedback projections from higher areas and the local connectivity within an area (see Figure 1.8). Previous findings have lent indirect support for either one of these scenarios (Churchland et al. 2010; Cohen and Maunsell 2009; Ecker, Berens, Cotton, et al. 2014; Gawne and Richmond 1993; Gu et al. 2011; Kara, Reinagel, and Reid 2000; Nienborg and Cumming 2009; Ruff and Cohen 2014; Schölvinck et al. 2015; Shadlen and Newsome 1998; Smith and Kohn 2008; Smith and Sommer 2013). Thus, shared neural variability appears to derive from multiple, parallel mechanisms that are not yet fully understood and ultimately, the origin of noise correlations is not yet known.

Noise correlations in V4 without V1

The range of mean values for noise correlations previously reported in visual area V4 for awake macaques range between 0.04-0.05 (Cohen and Kohn 2011). Most of these values likely come from layer 2/3 and there is some evidence that noise correlations are even lower in the input layer 4 (Rosen-

baum et al. 2016). As discussed above the origin of noise correlations is currently unknown. To add knowledge to this field, in chapter 2, I examine how noise correlations in area V4 changed after the removal of V1. While only a small percentage of the input to V4 comes directly from V1, the removal of V1 causes the loss of most of the feedforward drive to V4 as shown by huge reduction in responses to visual stimuli and minimal blood-oxygen-level dependent (BOLD) activity in V4. If noise correlations are a result of shared feedforward input then we would expect them to decrease without area V1 input. If instead noise correlations are due to feedback or recurrent connections then we might expect them to stay the same. If feedforward input acts to desynchronize activity between neurons then noise correlations might increase. I further investigated the structure of the noise correlations that I found and examined different timescales to gain further input into what properties of noise correlations in V4 changed after a V1 lesion.

1.3 Reward related activity

Reward is a complex phenomenon. Many things may be found by an organism to be rewarding, ranging from sugar water to a brand new car. In layman's terms the word "reward" can be used for anything that is perceived to be a "good" outcome. Interestingly this can change from moment to moment. For example, something that is initially rewarding may become non-rewarding once you've had too much of it, i.e. drinking water when you're thirsty is highly rewarding but not at all when you're no longer thirsty (Yamada et al. 2013). Most generally we can say that reward is a feeling produced by the brain when the organism does something that should help it survive and or reproduce. Some stimuli become rewarding through learning, for example you may have learned that money can buy you water when thirsty so acquiring money becomes rewarding. Certain drugs are also intrinsically highly rewarding, they stimulate the reward system directly and so may be preferentially taken rather than water when thirsty (Dackis and Gold 1985). Reward is a strong motivation for animals to perform certain actions and has effects on both learning and memory.

Traditionally the ideas of reward were interesting to early economists. They came up with a construct, *utility*, to try to explain the choices of individuals as maximizing a "desire" or "want" function, most famously written about by Bentham (1996). This could explain observations showing that people were willing to pay more money for a loaf of bread if they had none than

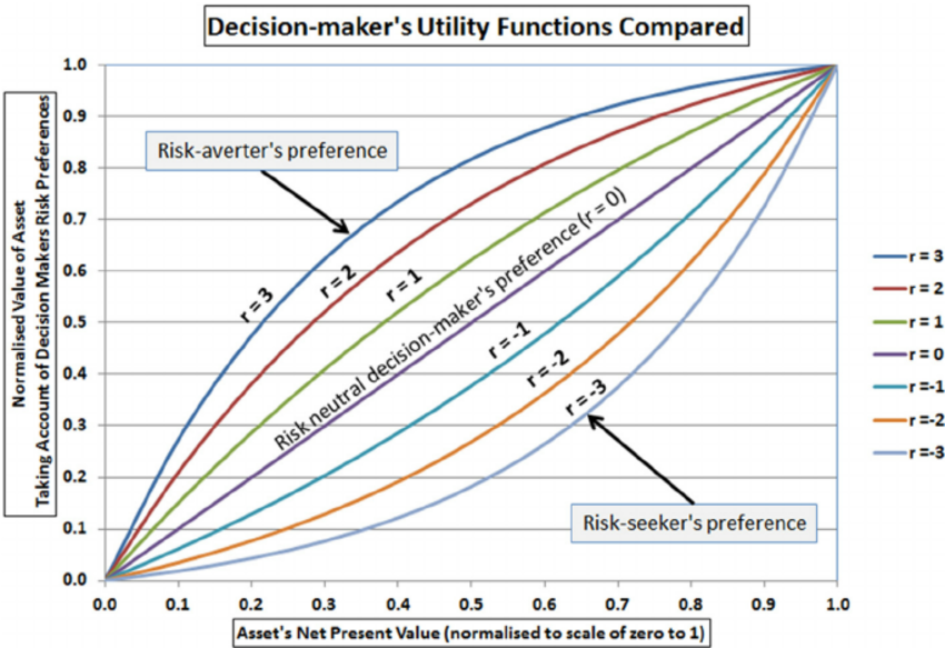

Figure 1.9 | An example of how utility functions change depending on different characteristics of the participant, in this case their risk aversion or risk seeking tendency. Taken from Figure 1 of D. A. Wood and Khosravanian (2015).

if they already had 10. From this perspective something is more rewarding if it has a higher *utility*. Economists have usually viewed utility as an inaccessible hidden variable that is individual to each person (Sen 1993). Someone might pay more for cheese than bread, but is internally consistent, if you like cheese more than bread and grapes more than cheese you also like grapes more than bread. Utility functions can also change with certain behavioral traits like risk behavior (see Figure 1.9).

More recently neuroscientists have started looking into similar questions. They found that the firing of dopamine neurons in the ventral midbrain are closely linked to the amount of reward expected by the organism (reviewed in Schultz, Dayan, and Montague (1997)). For example if you expected to receive 1 euro for a task and instead received 10 euros your dopamine neurons would fire very strongly. If however you instead received nothing your dopamine neurons would briefly stop firing completely. This is known as the Dopamine Reward Error Signaling (DRES) theory. Additional findings have shown that dopamine neurons and activity in the ventral midbrain correspond very well to theoretical ideas of utility. The firing of dopamine

neurons represents both the amount of reward and the probability of receiving it (Fiorillo, Tobler, and Schultz 2003), for example in the above scenario they would fire more during an uncertain choice if the probability of getting cheese was high. They also follow behavioral choice pattens that violate utility theory, for example loss aversion (Tom et al. 2007), which is the finding that people are less likely to take risks when they might lose something than when they might gain something.

As the role of dopamine in reward is almost undisputed, for understanding reward we should examine more closely the features of dopamine neurons. The dopamine response is phasic (see Figure 1.10). Initially neurons respond to any strong or *salient* stimulus and their firing rate is correlated to the strength of the stimulus. However, during the second phase of the response, reward related activity becomes the main determinant of their activity (Nomoto et al. 2010). The strength of their firing during this phase depends on the size of the expected reward. They also fire more strongly for rewards happening close to a cue stimulus and less and less when the time between the cue and reward becomes longer (Kobayashi and Schultz 2008). Then once the reward is actually received they change their firing based on the difference between the predicted (or expected) amount of reward and the reward that was actually given (Hollerman and Schultz 1998). These neurons innervate very diffusely through the whole of the cortex across all sensory modalities. Although it is not known exactly what these diffuse projections do, it is suggested that they are responsible for reward based learning and tying together all relevant features of a rewarded stimulus.

The use of macaques (*Macaca mulatta*) in experiments with reward has been vital because they are able to play simplified gambling style economic games as used in humans, with the advantage that brain activity with single neuron resolution can simultaneously be recorded from them. In the current study the task used to investigate reward related activity, as will be explained shortly, has not been used in any other species. Monkeys can also quickly learn associations between symbols and reward, and in addition relearn these associations as done in this study and, as mentioned previously, they have many homologous brain areas with humans. As the association of dopamine with reward has been preserved evolutionarily from flies through to humans (Liu et al. 2012), it is highly likely that the reward mechanisms investigated here are similar in humans and macaques which are even more closely evolutionarily related.

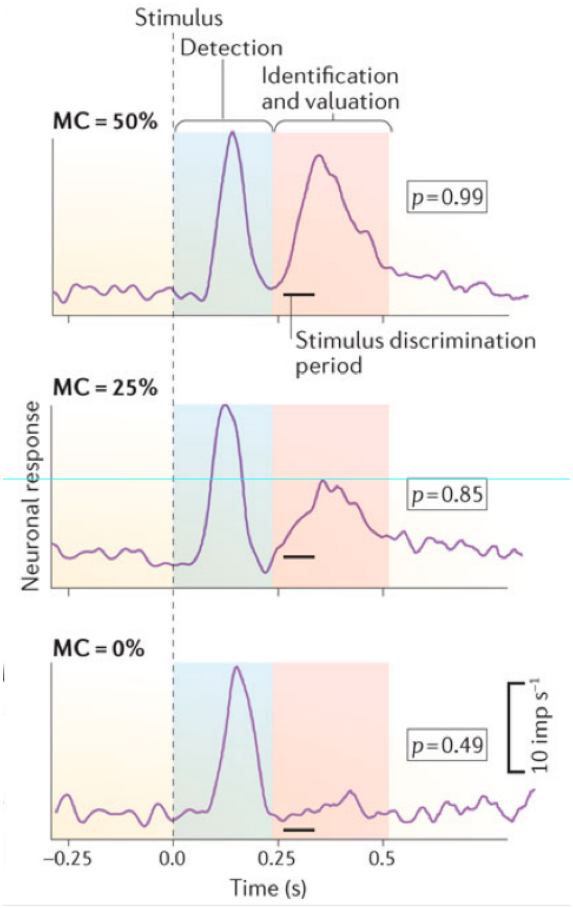

Figure 1.10 | The response of dopamine neurons varies with the probability of reward only in later stages. MC here stands for motion coherence which indicated to the monkey in which these cells were recorded what the reward probability would be. Taken from Schultz (2016) Figure 2.

Reward and decisions

While some features of reward responses are fairly well understood neurobiologically, it influences something far less well understood, decision making. Decision making for an organism is to make choices between different possibilities, for example choosing one tree for foraging as opposed to another. Another way to look at this is in the stimulus-response paradigm, where two trees are the stimuli and the response is to climb one tree as opposed to the other. While the trees can be seen as stimuli to be discriminated what is additionally being calculated is the likelihood and amount of reward (in this case fruit) supplied by each tree. Most previous work has been done on how decisions are made using the occulomotor system of macaques, as the brain areas related to eye movements were fairly well understood. The lateral intraparietal area (LIP), a cortical area involved in eye movements, was found to have neural responses related to reward based choices (Platt and Glimcher 1999) and most studies on the neural correlates of decisions have focused on the this area.

One study investigated how perception and reward interact to effect choice related behaviors in LIP. Rorie et al. (2010) used a task in which monkeys had to detect the direction of motion of a random dot kinematogram (RDK) and saccade in the corresponding direction. They were then able to vary the coherence of the dot motion to change the perceptual difficulty of the task while simultaneously changing the reward bias of the monkey by using the colors of the saccade target to indicate which direction of motion would be more or less highly rewarded. I adapted this task to explore effects of reward and perception on neuronal responses in V4. Using this task Rorie et al. (2010) found that a reward difference in the targets caused LIP neurons with the high reward in their RF to start firing even before the RDK appeared. This implies that if LIP is indeed embodying a drift diffusion process that reward can cause a change in the starting point of the integration process for the perceptual information, i.e. causing a bias. This in turn would imply that lower sensory areas should not be affected by the knowledge of a reward bias for one or another direction on a particular trial.

Reward related activity in V4

Much previous literature has focused on the role of attention in modulating visual responses in area V4 (as discussed earlier in this section, for review see Roe et al. (2012)). However, more recently a study found evidence that

instead of *attention* related activity, the *absolute value of reward* modulated the responses of V4 neurons (Baruni, Lau, and Salzman 2015). Most previous "attention" studies used changes in the relative value of reward to elicit attention (Maunsell 2004), for example, a response to one stimulus is rewarded and the other is unrewarded or the probability of one stimulus being rewarded is much lower than the other.

In their paper Baruni, Lau, and Salzman (2015) investigate the responses of V4 neurons to both changes in the absolute value of reward and changes in the relative value of reward (see Figure 1.11). The firing rates of neurons were dependent on only the absolute value of the stimulus within the RF and were *not* modulated by the value of the reward outside the RF. In conditions where the high reward was identical both inside and outside the RF, the attention was split equally between the two locations. However, the firing rate enhancements were identical to the condition where there was high reward only in the RF and not outside, a situation where attention was directed only to the RF. This implies that previous studies of "attention" related firing rate enhancements could be due instead to changes in absolute reward. They additionally found that other neural signals previously associated with attention; power in the gamma band range increasing and trial by trial variability decreasing; were also found without "attention". This implies that all previously reported "attention" literature wherein "attention" was modified using differential reward could instead be due to the reward differences.

However, according to a conference poster, a similar study has been performed by Ghosh and Maunsell (2016) and found different results. Similarly to Baruni, Lau, and Salzman (2015) they gave either equal or unequal amounts of reward for two stimuli, one inside and one outside the RF. They found very different results, that unequal reward produced the highest firing rate for high reward within the RF and that there was a significantly lower firing rate when both stimuli were equally highly rewarded. In addition they found that this firing rate increase from high reward equal to unequal was very similar to a firing rate increase caused by making the discrimination more difficult, which actually lowers reward probability. This could explain the results of Baruni, Lau, and Salzman (2015) because the equal high reward condition could be harder than the unequal high reward condition depending on the strategy of the monkey. However, Ghosh and Maunsell (2016) did their attentional cueing in blocks while Baruni, Lau, and Salzman (2015) cued each trial. Block cueing allows the monkey to develop temporary strategies specifically for a particular stimulus/reward

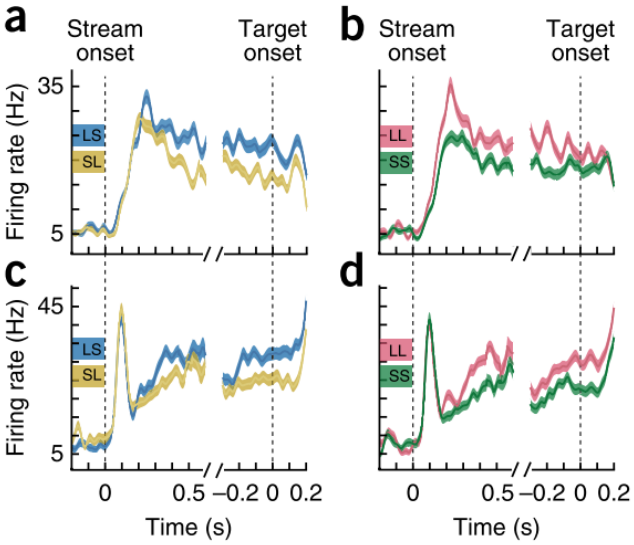

Figure 1.11 | Very similar effects on firing rate in V4 for attention and reward found by Baruni, Lau, and Salzman (2015). In this figure L stands for large reward and S stands for small reward. In two example neurons (a and c) there is a difference in the LS/SL conditions, which is like a classical attention task in that only one of the two stimuli are highly rewarded. However, in the LL and SS conditions (b and d) in which both stimuli are either highly or lowly rewarded with no difference in attention to either stimulus causes very similar changes in firing rate. Taken from Baruni, Lau, and Salzman (2015) Figure 2.

configuration and causes differences in expectancy (Posner, C. R. R. Snyder, and Davidson 1980). It may be that this encourages different strategies and so explains the differences in results between the two studies.

One fMRI study in non-human primates has examined reward related BOLD responses in visual areas while attempting to completely dissociate attention and reward. Arsenault et al. (2013) used a task in which some trials contained a reward after a visual reward cue but during others uncued reward was given. Each trial had a 50% chance of containing a reward (whether the visual cue appeared or not) but due to the unpredictable timing of the task the visual cue still indicated a strong increase in the probability of reward. During an uncued (and unpredictable) rewarded trial they found that the BOLD signal in the same areas that increased to the presence of a visual cue, showed a negative change (in areas V3, V4 and TEO). This result could not be due to attention as there was no visual cue present to attend to on those trials. They additionally found that using small amounts of a dopamine antagonist caused a smaller percent signal de-

crease after the uncued reward. This implies that dopaminergic responses after reward can cause changes in the activity in visual areas, and that this change is likely to be due to a suppression of neural responses (Shmuel et al. 2006). The finding of an increase in negative BOLD could be due to a more efficient representation of the stimulus causing less activity, as a previous fMRI study has shown that dopamine agonists decrease BOLD activity to a stimulus while increasing neural responses and the signal to noise ratio (Zaldivar et al. 2014).

Therefore, while there is some evidence that reward alone can increase the firing of V4 neurons, there are other studies that show it is more likely to be caused by attention, and one further study suggesting that suppression of neural activity may be linked to reward in V4. In chapter 3 I will attempt to clarify the effect of reward on V4 neurons by recording multiple V4 neurons in macaque monkeys using implanted Utah arrays and changing the reward conditions of a motion discrimination task on a trial by trial basis. I use a stimulus that is well encoded by V4 neurons but a feature discrimination determining the actual reward value that is unlikely to be performed by the V4 neurons. By changing the probability of the absolute amount of reward available on each trial, as well as the bias of the monkey to respond in a certain direction, I hoped to find an interaction between reward related behavior and absolute reward to clarify the issues outlined above.

Chapter 2

Noise Correlations

This chapter is heavily based on work previously published as Shapcott et al. (2016) which is openly accessible and published under a Creative Commons Attribution 4.0 International License. Some parts, in particular the discussion section, have been extended to suit the requirements of a thesis.

2.1 Methods

Subjects

Two healthy female *Macaca mulatta* with prior V1 lesions in the right hemisphere were used. All procedures were in accordance with the Institute for Laboratory Animal Research Guide for the Care and Use of Laboratory Animals and approved by the Animal Care and Use Committee of the National Institute of Mental Health.

Surgical procedures

The procedures used were as described in Schmid, Schmiedt, et al. (2013). A chronic 10 × 10 "Utah" array of microelectrodes (Blackrock Microsystems) was inserted into visual area V4. In a subsequent surgery, following the first period of recordings, an aspiration lesion was performed in V1

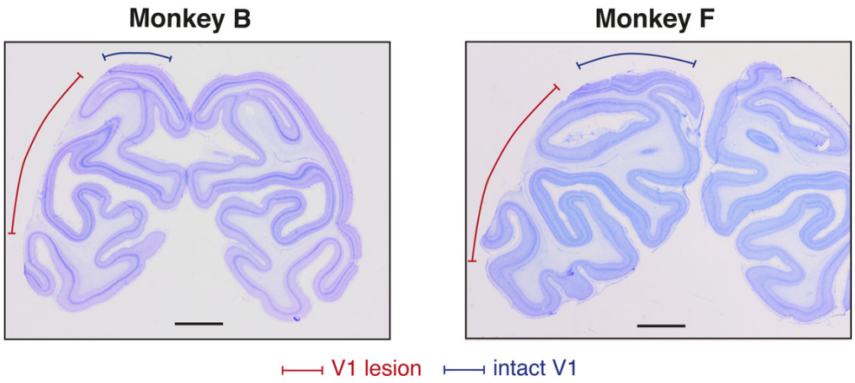

Figure 2.1 | Extent of the lesion in monkeys B and F
Coronal sections of area V1, dark purple is the staining of cortex which can be seen to be almost completely missing over area V1 in both monkeys after the aspiration lesion. Taken from (Schmid, Schmiedt, et al. 2013) Figure 1.

covering the central 7 degrees of the visual field. The extent of the lesion was confirmed in histology carried out post mortem (see Figure 2.1).

Array implantation

The left hemisphere that was studied here was intact at the beginning of the study. A large occipital bone flap over the left hemisphere was created to warrant access to areas V1 and V4. The "Utah" array was subdurally inserted on the prelunate gyrus, $\sim$ 2 mm dorsal of the lateral tip of the inferior occipital sulcus, near the entrance of the superior temporal sulcus. Each microelectrode was 1.5 mm long with a tip radius ranging from 3 to 5 μm, and an interelectrode spacing of 400 μm. After array implantation, dura and bone flap were sutured back in place and covered with the skin. Electrical reference was a wire located subdurally over the parietal cortex.

Behaviour

Monkeys completed a passive viewing task of which 800 ms was a baseline fixation period without visual stimulation, which was used for analysis. They had to maintain fixation within a 0.75° radius of a 0.4° fixation point, and after 3000 ms of fixation a variable amount of juice reward was delivered. Typically $\sim$80 of such trials were performed per session. Eye movements were monitored either using the scleral search coil technique or via infrared-based tracking of the pupil. Stimuli were presented with a

screen refresh rate of 60 Hz on a single LCD Samsung monitor (height 40 cm, width 65 cm) positioned at a viewing distance of 100 cm.

Neurophysiological recordings

We recorded from a random selection of 64 channels of the 96 channels available from the array. Electrode impedances ranged between 150 and 1 MΩ at 1 kHz. Extracellular voltages were amplified, filtered between 0.1 Hz and 12 kHz, and digitized at 24,414.1 Hz using a 64-channel RZ2 recording system (Tucker Davis Technologies).

Estimating MUA activity

For all MUA analyses we estimated multi-unit activity (MUA) using a technique validated by Supèr and Roelfsema (2004) (see Figure 2.2). To calculate this estimate the raw signal was bandpass-filtered between 300 Hz and 12 kHz with a fourth order zero-phase Butterworth filter, rectified, low-pass filtered at 120 Hz with a sixth order zero-phase Butterworth filter, then downsampled to 256 Hz. This yielded a quasi-continuous measure of high-frequency field power.

Data analysis

All data were analyzed with the MATLAB (R2011a, MathWorks) toolbox FieldTrip (Oostenveld et al. 2011) and custom-written analysis scripts. The significance of differences between pre and post lesion was assessed using a Wilcoxon rank sum test for all correlation analyses. Values reported in the text are median±interquartile range (IQR) for population measures and slope±standard error for linear regression if not stated otherwise in the text. The histograms were calculated using kernel density estimation with a normal kernel for display purposes. The bandwidth was chosen to be half of the optimal bandwidth for normal data to avoid over smoothing.

To calculate the Fano factor we took the spike count for each neuron on each trial and calculated the variance of these spike count per neuron and then divided it by the mean per neuron.

To calculate the coefficient of variation squared (CV^2) of the interspike intervals (ISI) we took the variance of the ISIs and divided it by the mean squared of the ISIs for each neuron on each trial. We then took the mean CV^2 across all trials to get one CV^2 value for each neuron.

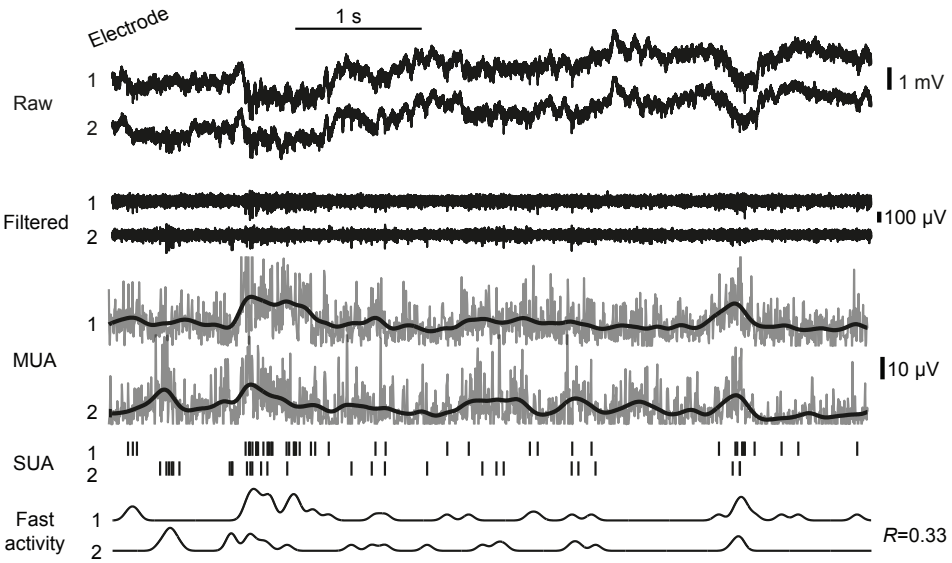

Figure 2.2 | Estimation of MUA and spike train correlation
Shown here are two simultaneously recorded electrode channels. Note that all signals show on-going variability, of which some is correlated between the two channels. Steps to calculate these signals from the raw data were as follows: To create MUA the raw data was band-pass filtered between 300-12000 Hz ("Filtered" in plot). This was then rectified and downsampled to create the MUA (gray line is the MUA, black line is the MUA smoothed). Short vertical lines are spikes extracted using a threshold (SUA). Note that the change in rate of these spikes closely follows the MUA. Spike train correlation was calculated by taking the convolution with a Gaussian window (standard deviation of 25 ms) of the spike train of two neurons ("Fast Activity") and calculating the correlation coefficient (Renart et al. 2010). In this example trial the fast correlation of the SUA was 0.33.

Single unit isolation

Unit activity was extracted by first high-pass filtering the signal with a median filter (0.5 ms window half-length) and then using a threshold of 1.3 SD. Units were isolated semi-automatically by first using the "KlustaKwik" algorithm (Harris, Henze, et al. 2000). Unit clustering was then manually refined by cluster cutting performed using "Klusters" (Lynn Hazan, Buzsáki lab, Rutgers, Newark NJ) with only well isolated units being categorized as single units 2.4. Only single unit pairs with a geometric mean firing rate of above 1 spike/s (Renart et al. 2010) were used for the analysis.

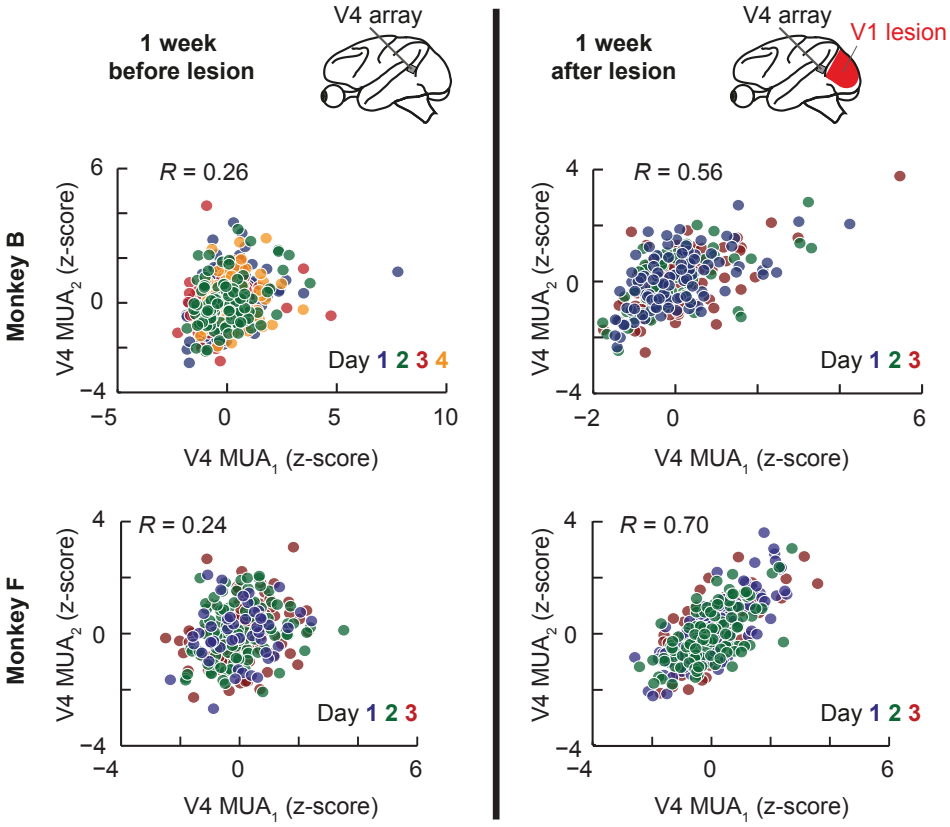

Figure 2.3 | Computation of rate correlations
Example rate correlation calculation. Shown is the z-scored MUA for channel pairs from monkey B and monkey F and the calculated Pearson's correlation coefficients. Colors indicate different recording sessions, which in days relative to the lesion (day 0) are for monkey B before lesion -6, -3, -2 and -1 and after lesion 4, 5 and 6 and for monkey F before lesion -4, -2 and -1 and after lesion 2, 4 and 6. Note that within pre and post lesion sessions points overlay, but between pre and post there is an increase in the correlation coefficient in these representative examples.

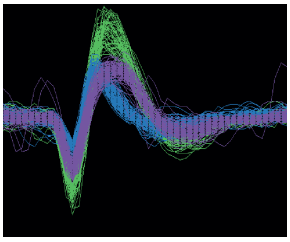

Figure 2.4 | Example single units from one channel
Waveforms of three single units, colored in green, blue and purple respectively, found on a single channel of the Utah array.

Computation of correlation coefficients

To calculate rate correlation the average of MUA activity over the initial 800 ms of baseline data in a trial was normalized through z-scoring by subtracting the mean of all the average MUA baseline values for that session and then dividing by their standard deviation. The Pearson's correlation coefficient between channels for these values was then calculated using the trial-by-trial data from all included sessions either pre or post lesion. For calculating the correlation coefficient over a short time window the baseline was divided into 16 50 ms segments and the average MUA activity calculated for each. To remove the influence of longer time scale rate fluctuation, the correlation across these segments was calculated for each trial and then averaged across all the trials of a session. This value was then averaged across all sessions in the week pre lesion and separately across all sessions in the week post lesion.

To compute spike train correlation methods were as used in (Renart et al. 2010). On each trial pairs of simultaneously recorded spike trains were first convolved with a Gaussian of standard deviation 25 ms to produce the "Fast Activity". The Pearson's correlation coefficient between these convolved spike trains was then calculated for each single trial. The instantaneous mean, calculated by convolving the spike train with a Gaussian of standard deviation 100 ms, was used in the calculation of the Pearson's correlation coefficient instead of the mean to remove influences of longer time scale fluctuations. Correlation coefficients were then averaged across multiple trials for a single pair to result in the spike train correlation value for a pair. The use of an instantaneous mean and averaging over separate trial segments should remove any correlations resulting from slow firing rate fluctuations on long time scales.

Microsaccade detection

Microsaccades were detected during the analysis period as in Engbert and Kliegl (2003) using code adapted from the Microsaccade Toolbox (Engbert, Sinn, et al. 2015). Microsaccades were defined as events with a velocity of over 5 standard deviations from the median on each trial and lasting for a minimum of 3 samples (15 ms for our eye data sampling rate of 200Hz). Detected microsaccades were rejected if they were within 50 ms of the previously detected microsaccade as overshoots or if the velocity was greater than 165 visual degrees per second as artifacts. The comparison of microsaccade number between pre and post lesion was assessed using a two-sample chi squared test.

Computation of Trial Cross Covariance (TCC)

The TCC was calculated as in Bair, Zohary, and Newsome (2001). The cross-correlation of the average MUA spiking activity was calculated for each session and then first averaged across all sessions pre lesion and then all sessions post lesion for each monkey. To calculate the long term component, the TCC at the 0 trial point was replaced with the mean of the -1 and 1 trial lag and then was smoothed with a Gaussian with a 4 trial standard deviation. This value of the smoothed line at trial 0 is the long term component of the correlation. To estimate the short term component of the correlation we subtracted the long term component from the value of the unsmoothed TCC at trial 0.

2.2 Results

In the present study we investigated the effect of surgically removing the primary sensory feedforward input, arising from area V1, on correlated firing of neurons in the primate visual cortical area V4. For the current analysis in V4, we hypothesized that if correlated firing were the result of a cascade of shared feedforward input alone, then removing the V1 input would be expected to decrease V4 noise correlations. To reduce the influence of stimulus induced effects, we sampled spontaneously occurring noise correlations in monkeys fixating a gray computer screen.

Trial-by-trial neuronal correlations

Our first goal was to test how much neuronal activity was correlated between V4 neurons on a trial-by-trial basis, that is, on correlations that occur over multiple seconds or longer and that are likely influenced by arousal and attention (Cohen and Kohn 2011). To test this experimentally, neurophysiological recordings were first made under intact V1 conditions, from electrode arrays chronically implanted in area V4. A surgical aspiration lesion was then subsequently performed in area V1 allowing measurement of V4 activity without V1 input. We analyzed data that were acquired while the monkeys visually fixated for 800 ms a small dot of light on a gray background of a computer monitor. To estimate interneuronal correlations, the average multi-unit activity (MUA) rate for each trial (Supèr and Roelfsema 2004) (see 2.1) was calculated for each electrode (see Figure 2.3). The correlation of these pooled values across trials was calculated for each electrode pair (n=1596 pairs in monkey B, n=1596 pairs in monkey F) to give two MUA rate correlation numbers per pair for each experimental session. This trial-by-trial MUA rate estimate within a session was pooled across each week before and after lesioning V1 until a maximum of 11 weeks (Figure 2.5).

One week prior to the lesion procedure (n=4 sessions in monkey B, n=3 sessions in monkey F), the median of the electrode pairs' noise correlations across sessions was similar in both monkeys (pre lesion median$\pm$IQR $=0.126\pm0.172$ for monkey B and 0.157 ± 0.205 for monkey F, Figure 2.5). After the lesion, correlations appeared overall quite similar across time points and monkeys compared to baseline conditions with V1 intact. Notably however, within the first week after the V1 lesion (n=3 sessions in monkey B, n=3 sessions in monkey F), correlations were increased compared to the week immediately pre lesion in both monkeys. This was par-

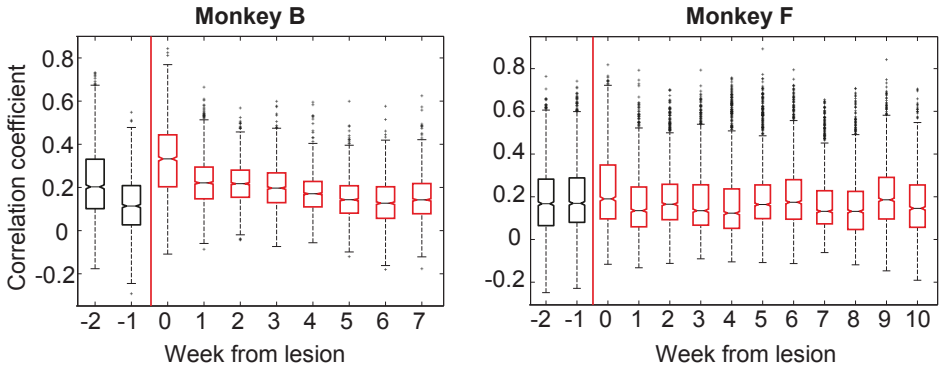

Figure 2.5 | Trial-by-trial V4 rate correlations pre and post lesion
Correlated firing over weeks. The correlation was calculated for each pair for each day and averaged over each week of the recordings. Boxplots show the distribution of all pairs each week. Week 0 is the week of the lesion. Note the increase in rate correlations in both monkeys the week of the lesion.

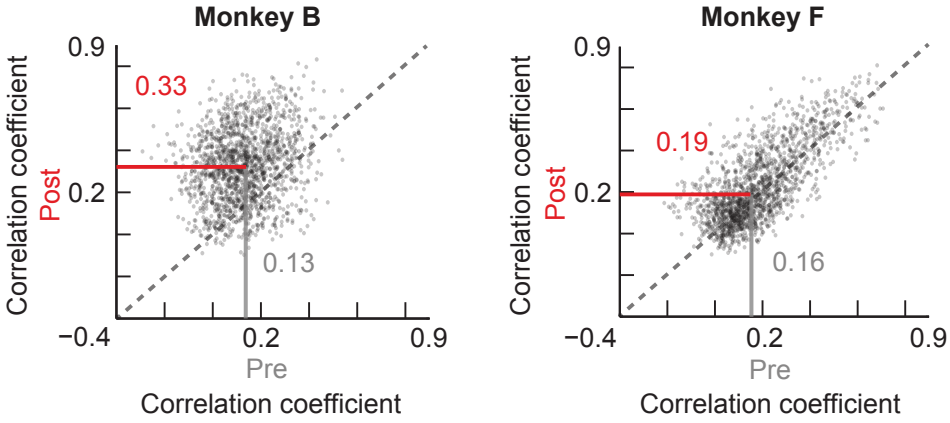

Figure 2.6 | V1 lesion causes an increase in trial-by-trial V4 rate correlation
Scatter plots of the rate correlation calculated for each channel pair 1 week pre and 1 week post V1 lesion (week -1 and week 0 in Figure 2.5). In both monkeys a highly significant shift upwards is evident. Median values are printed and indicated by the lines.

ticularly strong in monkey B (post lesion median±IQR=0.327±0.242), but was also present to a smaller extent in monkey F (0.186±0.251) (see Figure 2.6; Wilcoxon rank sum test; $p<0.001$ and $p<0.001$, respectively). However, in monkey F other week-to-week increases post-lesion were larger than the increase from pre to post lesion. In everything that follows, we focus our further analysis on this increased correlated variability during the first week after lesioning V1 compared to the week pre lesion.

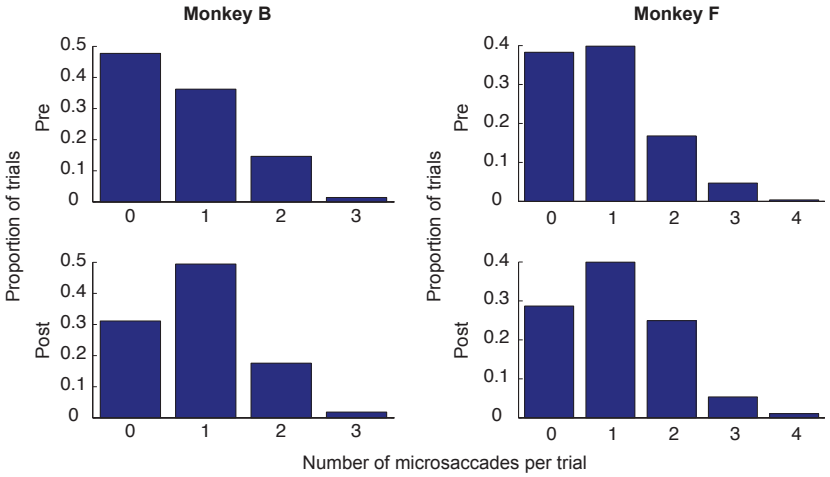

Figure 2.7 | Fixational eye movements increase in one monkey from pre to post lesion
Bar plots of the proportion of trials with different numbers of microsaccades pre and post lesion. Only in monkey B is there a significant change from 1 week pre to 1 week post lesion (chi-squared test; monkey B, $p<0.05$ and monkey F, $p=0.444$).

To investigate where this noise correlations increase could have come from, in a first step, we checked that increased noise correlations were not due to a lesion-induced systematic change in fixational eye movements. While in one monkey there was a significant increase in the number of microsaccades per trial, in the other monkey there was no significant increase(see Figure 2.7). Since there was a mean increase, we controlled for this by recalculating the the correlations both pre and post lesion using only trials in which just one microsaccade was present (see Figure 2.8). We found qualitatively similar results to those found using all trials, demonstrating that the increase was not due to changes in fixational eye movements.

We additionally still observed increased trial-by-trial correlation post lesion after removing the effects of long term correlations over multiple trials. We did this by calculating the trial cross-covariance (TCC) for both pre and post lesion (see Figure 2.9), and then examining the increase for the long and short components separately (see Figures 2.10 and 2.11). For both the single trial component ($\sim$ 3 seconds) and the multiple trials component ($\sim$ 4 trials) there was an increase from pre to post lesion.

From the above analyses we can therefore conclude that correlated neuronal activity in V4 was not only present in the absence of feedforward input from V1, but that it displayed a surprising increase in at least one

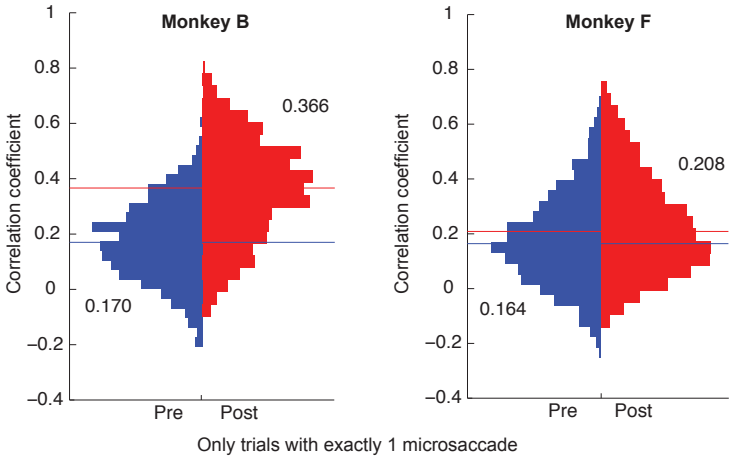

Figure 2.8 | Fixational eye movements do not cause correlation increase post lesion
Recalculated interneuronal correlation coefficients using only trials with one microsaccade (the mode for both monkey B and F). The results are qualitatively similar to those in Figure 2.6: in both monkeys there is a significant correlation increase from pre to post lesion (Wilcoxon rank sum; $p<0.001$ and $p<0.001$). Lines and values are the medians for pre and post, respectively.

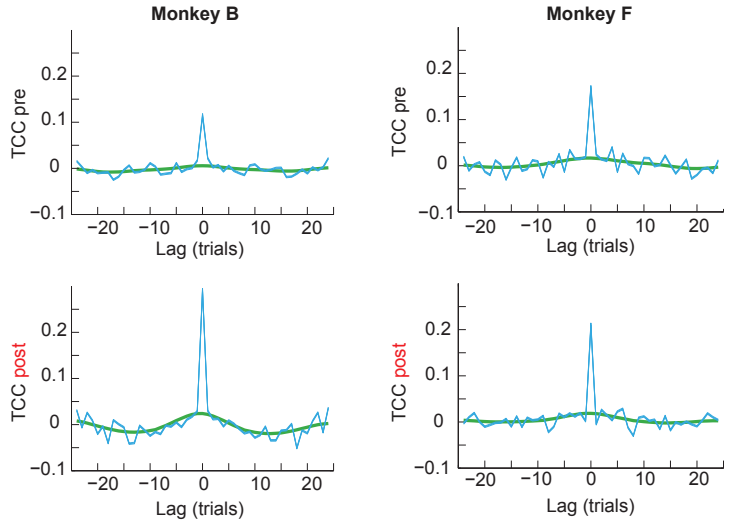

Figure 2.9 | TCC shows most correlation is within single trials
Plot of trial cross-covariance (TCC) for pre and post lesion as used by Bair, Zohary, and Newsome (2001) to examine correlations over time periods greater than one trial. The blue unsmoothed line is the TCC for pre and post lesion, see Methods (2.1) for calculation. The sharp central peak shows that most correlation is due to correlation within a time scale of one trial ($\sim$ 3 seconds average trial length). The smooth green line is a measure of the long term correlation arising over the course of around 4 trials ($\sim$ 12 seconds) see 2.1 for calculation.

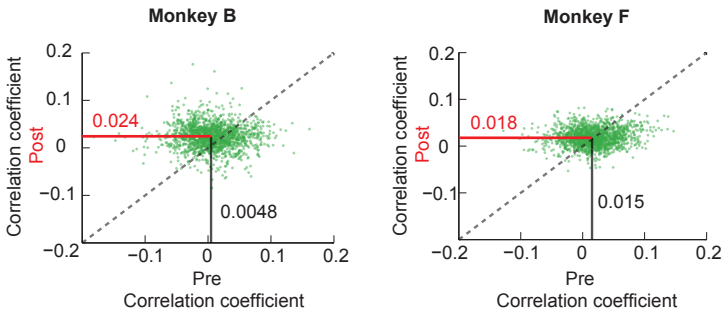

Figure 2.10 | The long term component of trial-by-trial interneuronal correlations increases from pre to post lesion
Long term ($\sim$ 4 trials) correlation contribution significantly increases in both monkeys from pre to post lesion (Wilcoxon rank sum; monkey B, $p<0.001$ and monkey F, $p<0.01$) despite being a small contribution to the correlation. Lines and values are the median for pre and post, respectively.

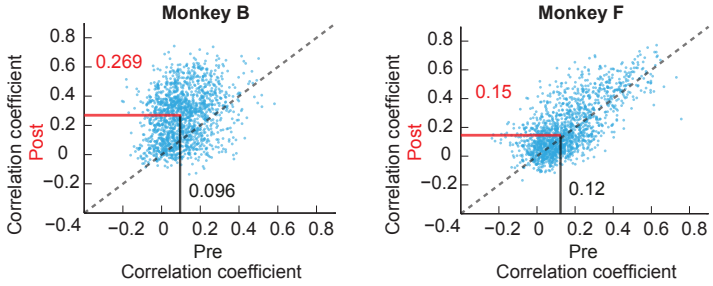

Figure 2.11 | The short term component of trial-by-trial interneuronal correlations increases from pre to post lesion
Short term (1 trial) correlation contribution also significantly increases from pre to post lesion (Wilcoxon rank sum; $p<0.001$ and $p<0.001$). Short term contribution is estimated by subtracting the long term component from the peak of the TCC at trial 0. Note the larger contribution of the short term component shown by the change in axes scale. Lines and values are the medians for pre and post, respectively.

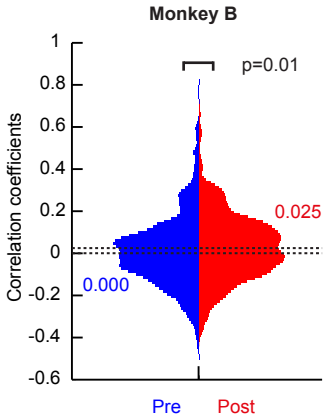

Figure 2.12 | Single unit trial-by-trial spike count
Single unit trial-by-trial spike count correlations increase from pre to post lesion. This is significant when tested with Wilcoxon rank sum test (p=0.011). Lines and values are the median pre and post correlations for single unit pairs assessed in monkey B.

monkey compared to conditions with intact V1 input during the first week after lesioning V1 which was not due to fixational eye movements or long timescale fluctuations in activity.

Further, correlations also increased from pre to post lesion for spike count correlations between single-unit pairs assessed in monkey B (see Figure 2.12). Spike count correlations are based on sum of activity within a trial of sorted single units. While the magnitude of these single-unit correlations is far weaker than those of the multi-unit, however, it is of similar magnitude to previously reported values for single-units with very low firing rates (see Figure 2.14 insert) (Ecker, Berens, Keliris, et al. 2010; Renart et al. 2010). In line with the MUA finding, single-unit correlations significantly increased from pre to post lesion.

Neuronal correlations as a function of cortical distance

It is known that neurons share more common feedforward input with their immediate neighbors than with neurons that are more distal (Blasdel and Lund 1983; Leopold, Murayama, and Logothetis 2003; Smith and Kohn 2008; Smith and Sommer 2013). This is thought to contribute to the falloff in correlated activity as a function of cortical distance (Leopold, Murayama, and Logothetis 2003; Smith and Kohn 2008). We therefore wondered whether this cortical distance function of correlated activity would change in V4 following the V1 lesion. To this end, we first plotted the pre

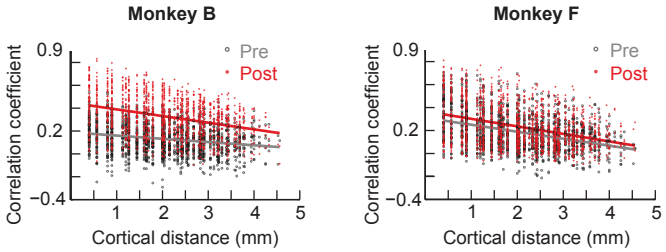

Figure 2.13 | V1 lesion causes an increase in trial-by-trial V4 rate correlation
Rate correlation with channel distance for pre and post lesion. Two separate linear fits for data 1 week pre and 1 week post V1 lesion are plotted over the data points. Note that the slope is negative both pre and post lesion in both monkeys.

lesion MUA rate correlation values against the distance between electrodes (Figure 2.13). This analysis confirmed the expected falloff of correlated activity with distance during V1 intact conditions: A linear regression fit to the pre lesion data showed a significant inverse relationship between correlation and interelectrode distance with a slope of -0.028±0.003 μm^{-1} in monkey B and a slope of -0.061±0.004 μm^{-1} in monkey F (F-test(1,1594); $p<0.001$ and $p<0.001$, respectively). Interestingly however, the resulting distance function persisted after the lesion, indicating that this feature of noise correlations could not derive either directly or indirectly from V1 feedforward input (Figure 2.13): After the lesion, not only was a similar falloff present, but the slope became steeper reaching -0.058±0.003 μm^{-1} in monkey B and -0.066±0.004 μm^{-1} in monkey F (F-test(1,1594); $p<0.001$ and $p=0.001$, respectively). The slope steepening following the lesion was significant for monkey B (ANCOVA interaction (1,3188); standard error = 0.003; $p<0.001$), but not for monkey F (ANCOVA interaction (1,3188); standard error = 0.003; $p=0.403$). The finding that trial-by-trial correlations persist in the absence of feedforward input and that they maintain their spatial specificity is in line with the view that such correlations are induced by fluctuations in attention or arousal (Cohen and Kohn 2011; Harris and Thiele 2011).

Within trial neuronal co-fluctuation

The results presented so far revealed how spiking averaged over an 800 ms time-window was correlated between electrodes on a trial-by-trial basis before and after removing feedforward input from V1. These correlations therefore reflect influences that occur over the course of seconds or slower and are likely influenced by behavioral or brain state (Cohen and Maunsell

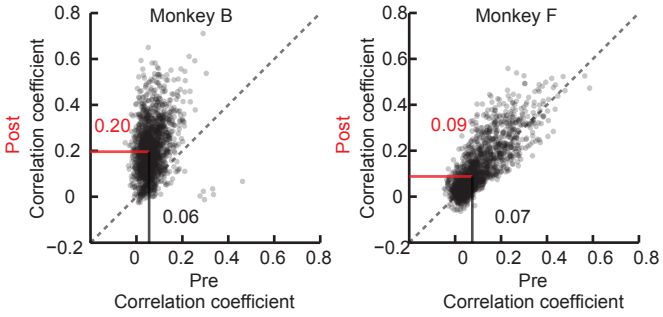

Figure 2.14 | V1 lesion causes an increase in short timescale MUA correlations
Scatter plots of the short timescale MUA rate correlation calculated for each channel pair pre and post V1 lesion. In both monkeys a highly significant shift upwards is evident. Median values are printed and indicated by the line.

2009). But correlations in neuronal activity also arise much faster, on the millisecond time-range within a behavioral trial, likely reflecting the local processing of cortical neurons. We therefore extended our analysis on correlated activity to the fast activity changes that occurred within the 800 ms fixation period. To this end we measured the average MUA during 50 ms wide time windows and assessed the extent to which MUA spiking changes were correlated between electrode pairs within the trial until the end of the 800 ms long fixation period. We found again that prior to the lesion, the median of the electrode pairs' short timescale correlations were similar in both monkeys (median±IQR=0.058±0.057 for monkey B and 0.074±0.112 for monkey F, Figure 2.14). After the V1 lesion, as found in the other analysis, there was a significant increase in within trial rate correlations among different electrode sites in V4, which was again particularly strong in monkey B (0.1971±0.151), but was also present in monkey F (0.089±0.151) (Figure 2.14; Wilcoxon rank sum test; $p<0.001$ and $p<0.001$, respectively).

To obtain a more direct measure of correlated within-trial neuronal activity, we additionally performed spike train correlations on 92 single units (897 simultaneously recorded pairs) pre lesion (days -8, -2 and -1 relative to lesion) and 83 single units (768 simultaneously recorded pairs) post lesion (days 4, 5 and 8 relative to lesion) in monkey B. This analysis was again done on the data recorded while the monkey fixated a small point on an otherwise gray screen. We assessed the correlation of single unit activity (SUA) convolved with a 25 ms standard deviation Gaussian and averaged over trials (Renart et al. 2010). Only well isolated single units were used

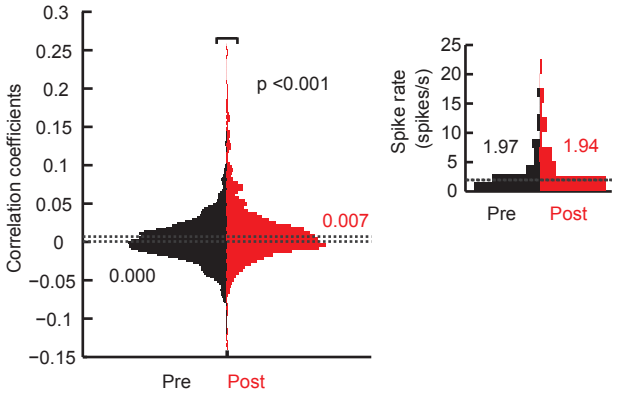

Figure 2.15 | V1 lesion causes an increase in SUA correlations
Histogram of SUA correlation coefficients pre and post lesion. Histogram is the kernel density estimation. Inset is spike rate distribution pre and post lesion. Median values are printed and indicated by the line.

for the analysis. Correlations were again found to be significantly increased post lesion. Spike train correlations increased from 0.001±0.031 pre lesion to 0.007±0.033 post lesion (Figure 2.15; Wilcoxon rank sum; p<0.001). When neuron pairs were binned by their geometric mean firing rate (Figure 2.16) correlated spiking from pre to post lesion was significantly increased in all but the first and last bins (Figure 2.16). Importantly, the overall single unit spike rates of neurons used to calculate the spike train correlations (see 2.1) were not significantly different from pre (1.87±2.86 spikes/s) to post (1.97±5.47 spikes/s) lesion (Wilcoxon rank sum; p = 0.342).

Similarly, the variability for all neurons did not change from pre to post lesion when measured by the Fano factor or the squared coefficient of variation of the ISIs (CV^2). The Fano factor was median±IQR=1.85±0.851 pre lesion and 1.97±0.850 post lesion (Wilcoxon rank sum; p = 0.174), while the CV^2 was 0.715±0.473 pre lesion and 0.764±0.332 post lesion (Wilcoxon rank sum; p = 0.1355). However, as there were only 14 of 92 single unit neurons pre lesion and 22 of 83 single unit neurons post lesion with an average firing rate greater than 5 spikes/s (as recommended in Nawrot et al. (2008)); this may therefore not be a reliable measure of the true variability within this dataset. In conclusion, our results on the correlated variability that occurs at short timescales extend and confirm our observations on the trial-by-trial based analysis, namely that correlated neuronal activity on both time scales persists in V4 despite the absence of V1 feedforward input.

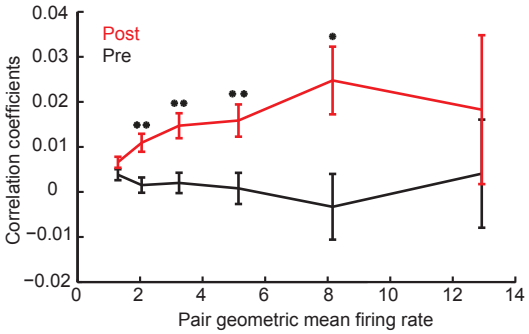

Figure 2.16 | V1 lesion causes an increase in MUA and SUA time course correlations
Average correlation coefficients for SU neuron pairs binned by the pair geometric mean firing rate. Error bars are SEM. Note that the spike train correlation from pre to post is increased in all bins. Stars show significance levels, **p<0.01, *p<0.05. For each bin the Wilcoxon rank sum one-sided test was run, p values respectively were; p=0.079, p<0.001, p=0.002, p=0.005, p=0.025, p=0.439; Ns respectively were; n(pre,post)=(252,192), n=(276,164), n=(214,160), n=(115,141), n=(34,79), n=(6,29).

2.3 Discussion

In this study we have shown that a lesion to the primary visual cortex, through which almost all visual information enters cortex, and which projects directly and indirectly to V4 among other areas (Nakamura et al. 1993), leads to an increase in correlated noise in V4 in one monkey, and no change or a small increase in another. The increase was found in MUA at both long and short timescales and in SUA for different firing rate ranges, and without an increase in the overall spike rate magnitude and Fano factor pre to post lesion, i.e., effects that could cause correlation increase (Rocha et al. 2007; Schmid, Schmiedt, et al. 2013; Smith and Kohn 2008). This result is surprising, as correlated neuronal firing is often at least in part thought to result from a cascade of common sensory feedforward input (Ecker, Berens, Keliris, et al. 2010; Gawne and Richmond 1993; Shadlen and Newsome 1998) and V4 correlated activity would therefore be predicted to decrease after a V1 lesion (see Section 1.2). Our results however, argue against such a scenario. Thus, noise correlations in higher-level cortex, at least in V4, cannot be explained on the basis of feedforward sensory input from V1 alone. What might be the sources of correlated activity if it remains without feedforward mechanisms and why did we observe a correlation increase in at least one monkey following the removal of V1 input?

Previously, Ecker, Berens, Keliris, et al. (2010) suggested that elevated firing correlations may result from slow trial-by trial drifts of neuronal excitability due to varying levels of alertness or arousal. However, such slow modulations are unlikely to explain our results alone, as we have found the increase simultaneously on timescales of less than 800 ms and more than 5 seconds. Other influences on correlated firing might instead comprise aspects of the local microcircuit or secondary input from other cortical as well as subcortical structures. Changes in the local microcircuit, in the context of our experiments, may be due to intrinsic plasticity caused by the altered input situation (Das and Gilbert 1995) or due to selective strengthening of certain components, for example local horizontal connections (Baseler, Morland, and Wandell 1999), which have been suggested to cause short timescale neuronal correlation within V4 (Smith and Kohn 2008; Smith and Sommer 2013). Alternatively, feedback from higher cortical areas in particular has been suggested to be an important factor in controlling correlation levels based on findings that noise correlations in V4 depend on the extent of top-down cognitive engagement during attention and learning tasks (Cohen and Maunsell 2009; Gu et al. 2011; Nienborg and Cumming 2009; Ruff and Cohen 2014).

In one monkey we found an unexpected increase in noise correlations after the lesion. There are several alternative ways to envision the state in the lesioned cortex that would explain this result. In this scenario neurons no longer receive strong external drive. The generalized balancing of inhibition and excitation (Atallah and Scanziani 2009; Xue, Atallah, and Scanziani 2014) could cause neurons with little drive to be have a membrane potential close to threshold, causing them to spike to any input that they might receive. This would make them highly likely to respond to input of any type, whether it is received from feedback, local interneurons or feedforward from other areas. While this feature alone does not explain why the neurons should be correlated one can image that in this case a small subthreshold excitatory synaptic potential (ESP) coming into multiple neurons at once, which would usually be drowned out by other activity (Das and Gilbert 1995), is enough to cause concurrent spiking.

When instead considering a longer time frame, like the seconds between trials used to calculate rate correlation in this study, fluctuations in inputs on a longer time frame must be considered. Fluctuations in cognitive state occur on a relatively long timescale, for example, the application of endogenous attention takes at least 300 ms and higher states of attention have been seen to be maintained for at least 10 trials before a correct trial

(Cohen and Maunsell 2010). Changes in alertness fluctuate with a period of ∼4 minutes (Lüdtke et al. 1998) and very slow changes in vigilance occur between 8-30 minutes (Conte, Ferlazzo, and Renzi 1995). Perhaps in the lesioned cortex non-specific activation arising from such slow inputs have greater effects due to the lack of competing driving input.

Feedback, local network activity and long range feedforward are the main candidates for determining correlation levels (see Figure 1.8). Feedback has already been suggested to be an important factor in controlling levels of noise correlation in studies showing that correlations can increase or decrease flexibly depending on the presence or absence of attention and learning (Cohen and Maunsell 2009; Gu et al. 2011). However, local connections in V4 can reach up to 6-8mm (Barone and Batardiere 2000; Yoshioka, Levitt, and Lund 1992) and it is within the whole of this range that we have found the observed increase, while feedback connections would be more widely dispersed. Perhaps external input to the cortex is actually desynchronizing and the act of removing this causes increased synchronization as seen in models of neural networks (Burwick 2009). Previously, the strengthening of horizontal connections in similar lesion situations (Baseler, Morland, and Wandell 1999) has been proposed to explain particular shifts in cortical representations in V2 post a V1 lesion. Additionally, it is possible that feedforward input from alternative sources becomes more important after a long term lesion. While monkeys showed a strong behavioral deficit post a V1 lesion, neural responses in V4 within the scotoma were found still to be present and were only fully abolished after LGN inactivation (Schmid, Mrowka, et al. 2010). This demonstrates an alternative pathway that may cause synchonisation of spiking, although as with feedback inputs, the inputs from thalamic regions are widely dispersed and additionally very few (Barone and Batardiere 2000).

In the context of the current experiments it is conceivable that top-down or feedback influences may have contributed to our results in several ways. At the behavioral level, it is important to keep in mind that the strongest increase in monkey B was observed directly after the lesion, as was the small increase in monkey F. It is known that monkeys during this period are blind and cannot saccade to visual stimuli presented to the scotoma (Mohler and Wurtz 1977; Schmid, Schmiedt, et al. 2013; Yoshida et al. 2008). In line with the observation that noise correlations depends on the level of top-down engagement (Cohen and Maunsell 2009; Gu et al. 2011), the increase in correlated activity observed in the present study might therefore reflect the altered perceptual status of the monkeys immediately following the

V1 lesion. At the neural level, oscillations in the beta range have been recently reported as markers for cortical feedback signaling (Bastos et al. 2015; Van Kerkoerle et al. 2014). We have previously reported prominent alpha/beta oscillations (12-20Hz) in V4 following a V1 lesion (Schmiedt et al. 2014), perhaps indicating unmasked or upregulated feedback influences that could possibly contribute to the increase in V4 correlation levels we observed in the present analysis. While ultimately several scenarios shaping correlations seem possible at this point, we have shown that even with reduced feedforward sensory input, noise correlations remain substantial in extrastriate visual cortex.

Chapter 3

Reward Related Activity

3.1 Methods

Subjects

Two healthy male *Macaca mulatta* (macaques) aged 8-9 years and weighing 12-15 kg were used in the study. All procedures were in accordance with the animal welfare guidelines of the Regional Board Darmstadt (F149/05) and the European Union's Directive 2010/63/EU. The monkeys were housed in all male groups of 2-4 with access to both an outdoor and indoor area. Animals received controlled access to fluids to ensure motivation for the cognitive experiments in accordance with regulations and their individual body weights. Food was freely available at all times and water was provided on every day.

Surgical procedures

For each surgery anesthesia was induced by injections of ketamine and monkeys were intubated before the start of any other procedure. In an initial surgery, titanium headposts custom fit to each monkey's individual skull were implanted onto the front of the skull so that the monkey could be restrained during recordings of neurophysiological signals and eye-movements.

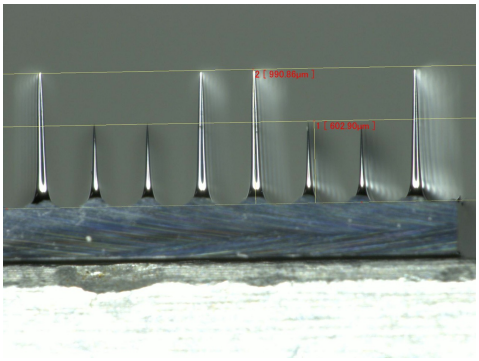

Figure 3.1 | Micrograph of array electrode lengths

A large occipital bone flap over the left hemisphere was created to warrant access to area V4. A Utah array (Blackrock Microsystems) was subdurally inserted on the prelunate gyrus, ∼5 mm dorsal of the lateral tip of the inferior occipital sulcus, near the entrance of the superior temporal sulcus. Insertion was performed using a pneumatic inserter (Blackrock Microsystems). Half the microelectrodes on the array were 1 mm and the other half were 0.6 mm long with a tip radius ranging from 3 to 5 μm, and an interelectrode spacing of 400 μm (see Figure 3.1). A connector attached to both arrays was implanted into the bone on the right hemisphere. After array implantation, the dura and bone flap were sutured back in place and covered with the skin.

Monkeys were given at least one week of holiday (no training or water restriction) after each surgery to allow for a full recovery. One additional surgery was performed to implant a thalamic chamber, but no data from this implant is reported here.

Stimuli presentation

The monkeys were placed in a dark and electrically isolated booth and then headfixed before each recording session. They were positioned ∼80 cm from a 22" LCD Samsung 2233RZ monitor running at 120Hz. This monitor was chosen due to its suitability for vision research and precise timing (Wang and Nikolic 2011). Most stimuli were presented on the monitor using the MonkeyLogic toolbox (Asaad and Eskandar 2008) with MATLAB 2011a (The Mathworks Inc.). The receptive field (RF) mapping stimuli were presented using Psychtoolbox (Pelli 1997) also running on MATLAB 2011a. This was run on a Windows 7 computer using a NIVIDIA graphics card.

Stimuli were square wave gratings of 1.5-3° (visual degrees) with a spatial frequency of 1°. Also displayed were colored dots to signify reward amounts and white bars to map the RFs.

Eye tracking

Eye movements of one eye were tracked using the infrared camera system Eyelink 2000 (SR Research Ltd.) powered by a 6 V battery. The eye movements of the monkey were calibrated on each day before any sessions were run. Stimuli were always presented on a gray background to get the best possible eye signals. The pupil size was also recorded throughout each session.

Receptive field mapping

RFs were mapped using a backprojected bar method (Fiorani et al. 2014). Bars the length of the entire screen and width of 1° were moved across the screen at 8° per second. Eight directions of movement were tested using four bar orientations. The location of the start of neural responses to the bar in each direction of motion was used to make an estimate of the size of the RF for each channel in very little time (approximately 5 minutes). RF centers for both monkeys are shown in Figure 3.2.

Behavioral task

Monkeys completed a motion discrimination task. One example trial of the basic motion discrimination task is as shown in Figure 3.3. To start the trial the monkey had to begin fixating on the fixation point (within a 0.8-1° (visual degrees) radius of the central white dot). After a baseline period the static grating appeared as shown in the second panel of Figure 3.3. This stayed on screen for some time as the sensory control period. After this period the grating displaced between one frame and the next (∼8 ms at 120Hz). This appeared perceptually as a small motion event and the monkey needed to discriminate in which direction it was. The size of the displacement was varied between 3 and 11 pixels. The monkey needed to maintain fixation on the fixation point for a period afterwards, this was the saccade planning period. When the fixation point disappeared it signaled to the monkey that they could make a saccade to one of the saccade targets. In all versions of this task the monkey would *always* receive reward if they correctly discriminated the motion and saccaded in the corresponding direction. They would *never* receive reward if they indicated the incorrect

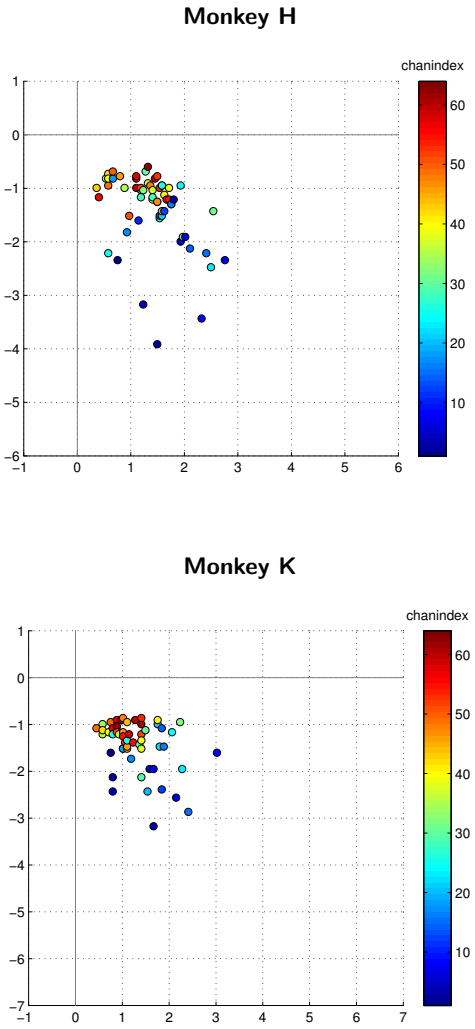

Figure 3.2 | V4 RFs Color scale shows the channel numbers going from the dorsal to ventral side of the array. Centers were determined using a moving bar swept across the screen and finding the maximum response.

motion direction. No data from this task is shown as it was only for training purposes.

In the more complex version of the motion discrimination task (shown in Figure 3.4) the reward value of the direction of motion was denoted by the color of the saccade target (either green or blue). One of the two colors would indicate *High* reward and the other *Low* reward. The low reward was always half the volume of juice given for the high reward by using a single or double pulse for low and high reward respectively. The colors of the saccade targets changed after the sensory control period as shown in Figure 3.4. Again monkeys had to correctly discriminate the direction

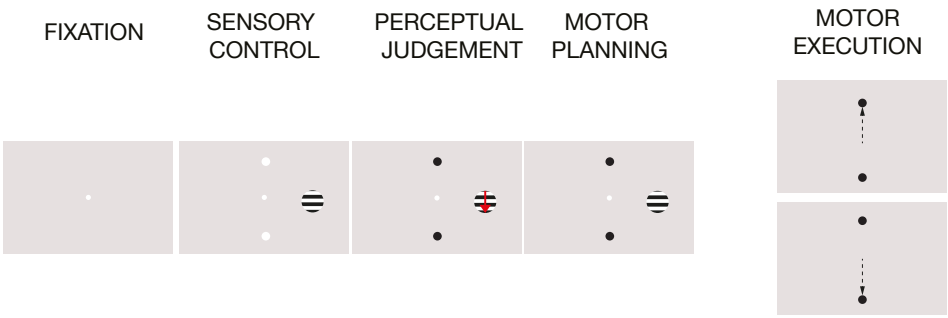

Figure 3.3 | The basic motion discrimination portion of the task
The monkey had to fixate on the fixation point (central white dot in figure) until it was removed. A static grating was then presented. Between one frame and the next a very small displacement (3-11 pixels) of the grating took place in either an upwards or downwards direction. This small displacement appeared perceptually as a small amount of motion. The monkeys reported the direction of the displacement by saccading to either the upwards or downwards saccade target (black dots in figure).

of motion of the grating in order to receive any reward. However, in this version the amount of reward they received depended on the color of the saccade target for that direction.

There were four conditions based on the reward values of the saccade targets; HH, HL, LH and LL (see Figure 3.5). In the naming of these conditions the first letter corresponds to the value of the downwards motion while the second corresponds to the value of the upwards motion. Conditions in which more reward was given for one direction than another produced biases, as predicted by reward optimization behavior previously reported in macaques (Feng et al. 2009). As expected, when the task was easy the biases were less pronounced, when the task was very difficult the reward biases almost completely determined the choice of the monkey (see Figure 3.7). The meaning of the color (whether it was high or low reward) was kept stable for one week and then switched on the next week. This allowed us to control for differences in responses due to color (because V4 is a color sensitive region (Tanigawa, Lu, and Roe 2010)). The task timings are shown in Figure 3.4.

In one session the cue was presented 600 ms before the onset of the stimulus. All other task parameters were kept the same.

Figure 3.4 | Motion discrimination task with reward
This task was very similar to the basic motion discrimination task (see Figure 3.3) but with a new reward judgment stage. The colored reward cues then stayed on for the duration of the task. It is important to note that reward was *only* given if the direction of motion was the same as the saccade direction. In this example condition blue would signify high reward while red is low reward, meaning a correct saccade upwards would give high reward while a correct saccade downwards would give low reward. The timings shown were those used for the recorded task.

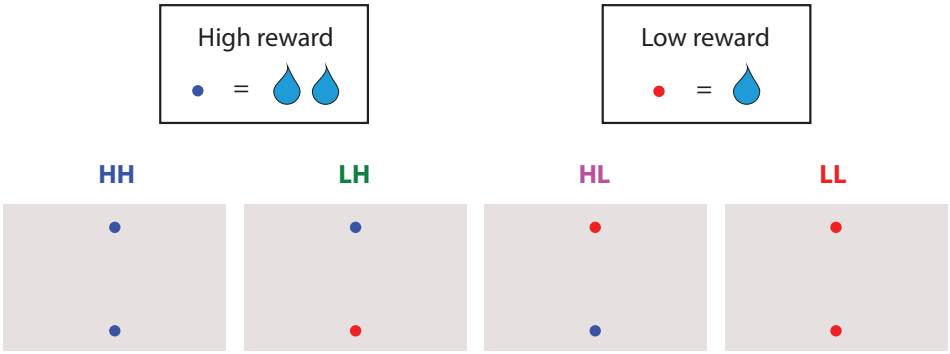

Figure 3.5 | Reward conditions
Four possible reward conditions were present in this task; HH, LH, HL, LL. This corresponds to the value of the saccade target, the direction of motion is irrelevant. The first letter of each condition corresponds to the value of the downwards motion while the second corresponds to the value of the upwards motion. Here the blue target is high reward and the red target is low reward. Condition colors are as used in figures throughout this chapter.

Neurophysiological recordings

Recordings took place in an electrically isolated booth with all necessary power coming from a 12 V battery. Utah array electrode impedances were between 70 and 800 kΩ at 1000 kHz. The 128 channels were amplified, filtered between 0.05 Hz and 10 kHz and digitized at 30 kHz directly at the connector using a CerePlex^{TM} E headstage (Blackrock Microsystems). Signals were then transfered out of the electrically isolated booth via optic fiber and recorded using a Cerebus^{TM} Neural Signal Processor (Blackrock Microsystems). A reference wire was placed under the dura towards the cerebellum and parietal cortex in both monkeys.

Estimating MUA activity

To obtain an estimate of multi-unit activity (MUA) (see Figure 2.2 (Supèr and Roelfsema 2004)), the raw signal was bandpass-filtered between 300 Hz and 30 kHz with an eighth order zero-phase Chebyshev filter, rectified, low-pass filtered at 120 Hz with a sixth order zero-phase Butterworth filter, and downsampled to 500 Hz, yielding a quasi-continuous measure of high-frequency field power.

Data analysis

All data were analyzed with the MATLAB (R2011a, MathWorks) toolbox FieldTrip (Oostenveld et al. 2011) and custom-written analysis scripts. The

significance of difference between conditions was performed with Wilcoxon rank sum tests per channel and the number of channels with significant differences are reported. Averages of arrays or single channel plots shown for display purposes were smoothed with a Gaussian. Error bars on all plots are standard error of the mean (SEM). For plots showing the mean array activity the average SEM across the channels is used. To baseline the data the mean and standard deviation of the average baseline activity were calculated and then these values were used to z-score the period of interest. Baselining was performed on each channel separately.

The population Fano factor was calculated using the mean and variance for each electrode on each session. A regression across the population was then performed weighted by the number of trials for each session to calculate the population Fano factor (Churchland et al. 2010). The significance of differences between these regressions between conditions was performed using a Z test.

Mean matching was done as in Churchland et al. (2010) by splitting the mean rates into bins for each time segment. These distributions were then matched across segments by taking the minimum number of trials for each bin across the segments and ensuring that all segments had this minimum trial number by randomly discarding trials in bins with more trials. The data points that survived the mean matching were then used for Fano factor calculations. This was repeated 50 times and the final value was the average calculated over the 50 repetitions.

Data pooling and selection

Only channels with an average sustained response to the grating stimulus of greater than 0.3 z-scores above the baseline were analyzed. Half of the data was designated green (G) and the other half blue (B). Green data within the HH and LL conditions were GG so that the visual stimulus was identical with only reward values differing. Similarly, green data within the LH and HL conditions were GB so that again the visual stimulus was identical with only reward vales differing. This means that within the green data HH and HL conditions came from the same sessions while LL and LH came from the same sessions. The same is true for blue data; only the colors are reversed. As the results from both colors were qualitatively similar, we pooled over green and blue for the plots and analyses presented here.

Data were baselined within each session but statistical tests were performed

on averages of trials pooled over all sessions performed. The trial numbers for each analysis window are given in Table 3.1. In the analysis of the cue before stimulus onset only one session was recorded in monkey K only and therefore there was no pooling of trials over sessions. For individual p values for each channel please see Section 4.3 in the Appendix.

Trial numbers

Pupil response

	HH	LH	HL	LL
Monkey H	664	580	785	902
Monkey K	1276	975	1162	1645

Stimulus onset, Cue onset, Choice probabilities

	HH	LH	HL	LL
Monkey H	1758	1623	1792	1841
Monkey K	1625	1547	1755	1855

Motion onset

	HH	LH	HL	LL
Monkey H	1359	1104	1340	1432
Monkey K	904	715	737	1090

Cue before stimulus

	HH	LH	HL	LL
Monkey K	218	198	211	166

Certainty

	Sure	Unsure
Monkey H	906	1538
Monkey K	315	1137

Table 3.1 | Number of included trials for each analysis performed for each monkey.

Calculation of neural responses

For each trial the average activity of each channel was calculated for late phase of the stimulus response (0.3 to 0.5 s post stimulus onset) and this value was subtracted from the cue related activity. For each pooled data set the average activity of this baselined data was calculated. The minimum of the suppression for each channel was found by taking the minimum of this average channel response between 0.1 to 0.3 s post cue onset. The suppression time was calculated as the time at which this minimum was reached for each channel. The motion response was calculated as the maximum

response in the period from 0.05 to 0.2 s post motion onset, baselined to the 0.5 s of data before motion onset.

Pupil analysis

For each session the pupil data was normalized to a percentage of the mean of the entire session while the monkey was fixating within the fixation window. On each trial the mean percentage during the baseline was calculated and subtracted from the rest of the trial, giving units of percent change. Due to the slow nature of pupil responses (Beatty and Lucero-Wagoner 2000) the analysis windows for the pupil data were 200 ms later than those for the neural data. Fewer trials were available to analyze the pupil data as in a few sessions experimenter error resulted in pupil values not being recorded. Trial numbers are given in Table 3.1.

3.2 Results

Reward information biases the decision criteria of subjects performing discrimination tasks. Here we investigated how reward affected the neural activity in the visual cortex during a discrimination task. We recorded neural activity in area V4 using implanted Utah arrays in two macaques previously trained on a motion discrimination task. This task was modified to include reward information; on each trial a colored reward cue informing the subject of the reward value of each motion direction. We hypothesized that when this cue indicated that high reward was available on a trial that this might cause an increase in the firing of V4 neurons during the task.

Behavioral bias with reward

We designed a task based on Rorie et al. (2010), which was a motion discrimination task in which variable amounts of reward were given based on the direction of the motion (see Figure 3.4). As in the Rorie et al. (2010) paper, the monkeys showed a bias towards the higher rewarded direction when there was differential reward available (see Figure 3.6). This was indicative that they understood the task and how to optimize reward amounts.

A binomial test showed that both monkeys were significantly more biased towards the higher rewarded target than would be expected by chance. For condition LH $p<0.001$ (n=2102) and $p<0.001$ (n=3058) for monkey H and monkey K respectively, for condition HL $p<0.001$ (n=2349) and $p<0.001$ (n=3231). Different amounts of motion were used to compute a psychometric curve, which shows that the monkeys had differing biases depending on the difficulty of the task (see Figure 3.7). Monkeys were more biased for difficult trials (small motion displacements) than easy trials (large motion displacements). After normalizing to the average behavior on each session it is possible to see that monkeys were worse at LH and HL conditions than HH and LL across sessions (see Figure 3.8).

Interestingly it can be noted (see Figure 3.8) that there is very little difference between percent correct for the HH and LL condition. The LL condition is even slightly higher, which may be surprising given that the LL condition had lower reward which should cause low motivation for the monkey. However, when examining the fixation breaks in each condition it can be seen that there are far more for the low reward condition, showing that monkeys gave up on that condition earlier as expected (Varazzani et

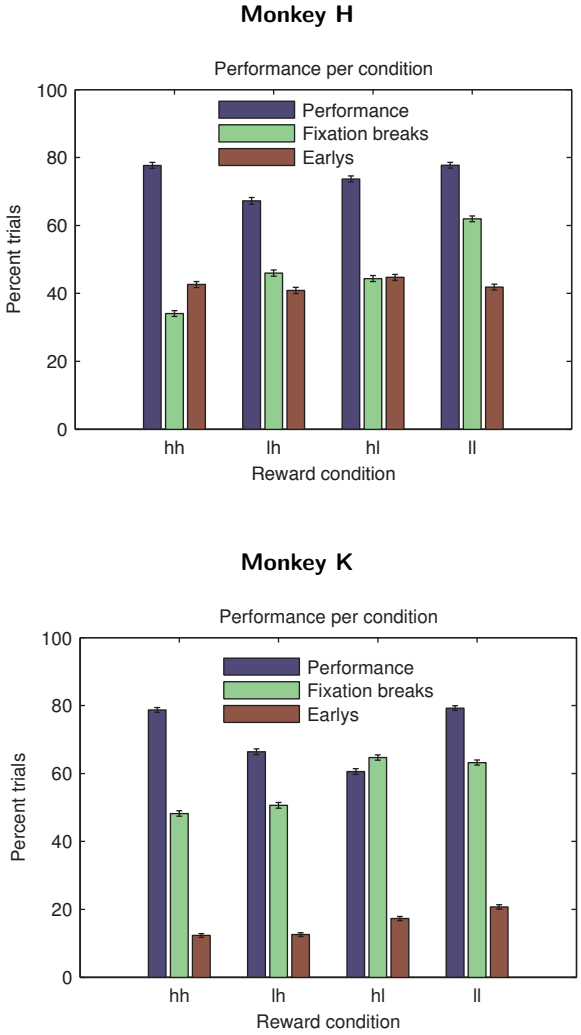

Figure 3.6 | Task related behavior split by reward condition
Performance (percent correct of completed trials), fixation breaks (percent of fixation breaks out of all trials) and early responses (percent of early saccades to one of the two saccade targets out of all trials). Note that the HH and LL conditions look very similar for performance but differences can be seen in the extent of fixation breaks.

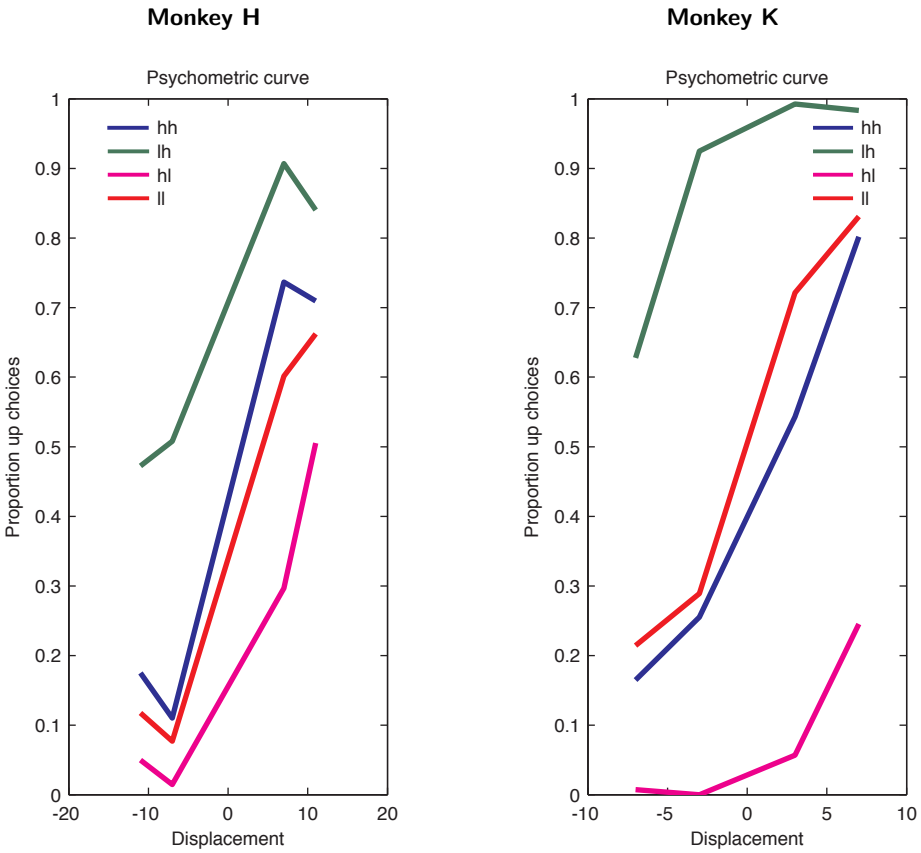

Figure 3.7 | Psychometric curve split by reward condition
Only two displacements were used but it is still possible to see that biases towards the more highly rewarded direction are increased when the task is more difficult. Positive displacements have correct responses in the upwards direction while the opposite is true for negative displacements. Trial numbers for each condition in the order HH,LH, HL and LL for monkey H are -11; n=1103,1014,1130 and 1140 -7; n=118,126,137 and 143 7; n=129,118,118 and 138 11; n=915,844,964 and 1018 while for monkey K these are -7; n=1185,1246,1361 and 1350 -3; n=286,239,266 and 270 3; n=267,263,282 and 330 7; n=1332,1310,1322 and 1408

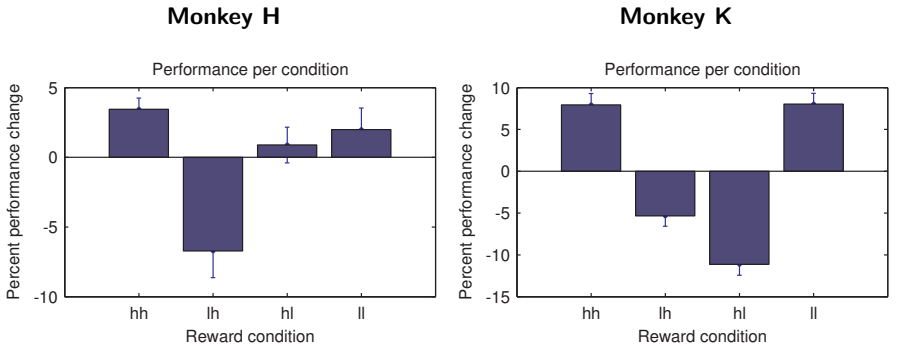

Figure 3.8 | Performance normalized to average
Difference from average session performance per condition averaged over n=14 sessions in monkey H and n=20 sessions in monkey K. Note that monkeys performed worse in the LH and HL conditions, on average, than in the HH and LL conditions.

al. 2015).

Pupil dilation with reward

As pupil size has previously been shown to be modulated by reward (Varazzani et al. 2015; Baruni, Lau, and Salzman 2015), we decided to examine pupil size in the different conditions. Pupil dilation reflects the activity of the sympathetic nervous system which correlates with the effort and arousal state of the monkey as well as outside factors like reward and task difficulty (Varazzani et al. 2015; Kahneman and Beatty 1966). Pupil responses take between 200-1000 ms (Beatty and Lucero-Wagoner 2000) and in our task a bright stimulus came on 400 ms before the cue so unfortunately the effect of the cue on the pupil diameter is contaminated by this light response. However, in Figure 3.9 it is possible to see that after the pupil stimulus response is finished, between 600-1200 ms post the cue onset there is a separation of the pupil size between the conditions. As previously reported, when there is low expected reward (LL) the pupil size is smaller than when there is high expected reward (HH). Strangely, in monkey H we also see a separation between LH and HL conditions, despite the expected reward being the same. But when looking at the performance (see Figure 3.6) it is possible to see that the monkey was indeed worse at LH condition, which would result in a lower reward for that condition. However, the reason that this condition was harder for that monkey is unknown as they were intended to be equivalent.

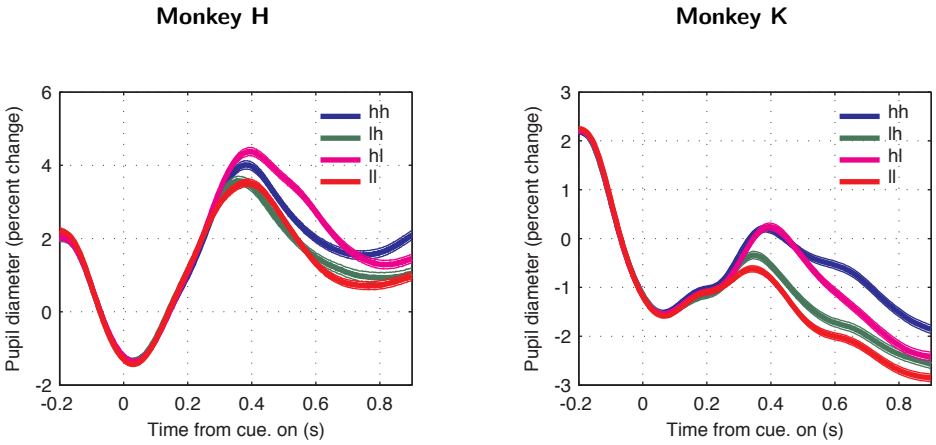

Figure 3.9 | Pupil response to cue onset
Pupil size is measured in percent change from the baseline. Note that while initially the pupil size is larger for HL in Monkey H after some time it does decrease below the HH condition.

Cue related suppression

We have shown that as expected reward difference had a strong effect on the behavior of the monkeys, and this effect was dependent on the visual input received. We next investigated if reward had a similarly strong effect on activity in visual area V4 of monkey visual cortex. To do this, we split the task into sections of interest. Stimulus onset is the initial period of the task when the gratings and white saccade targets appeared on the screen. We would not expect to see any difference with reward at this stage as there is no reward information available. This is indeed what we found, which is shown in Figure 3.10.

Cue onset is the first task period during which reward information was presented and could have effects on the neural data. However, as the cue information was presented far outside the RF of the Utah array (from 4 to 12° away) we initially did not expect to see large reward related changes in spiking activity. But when looking at spiking locked to the cue onset period in both monkeys we found a large reward related suppression effect (see Figure 3.11). As seen in this plot the presence of a cue indicating high reward caused much stronger suppression than a cue indicating low reward. A Wilcoxon signed rank test was used to test the significance of this suppression. Every channel in every reward condition was found to show a significant suppression compared to the post stimulus sustained response in both monkey H (58/58) and monkey K (31/31) (see Table 1).

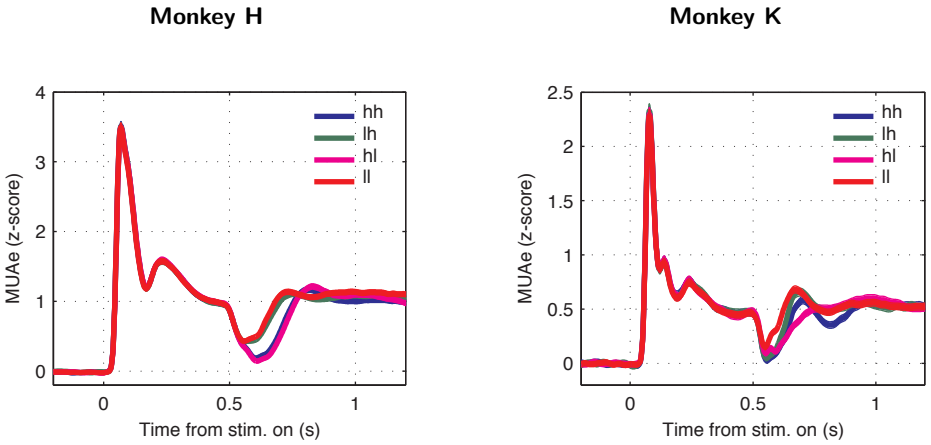

Figure 3.10 | MUAx response to stimulus onset
Initially, as expected, neural responses are similar for all conditions. Cue onset takes place at 0.4 s when a large suppression (almost to the level of the baseline activity) occurs. Plot shows the mean and SEM of activity across all included electrodes for each monkey.

In fact by looking at Figure 3.10 it is possible to see that during the HH condition, on average the MUA responses drop almost to the pre-stimulus baseline levels, when the monkey is looking at a blank gray screen. In monkey K (Figure 3.11) the presence of the cue indicating high reward even 12° away could cause the enhanced suppression (LH condition), while in monkey H only the nearer cue (4-8° away) caused this effect (HL condition). In the HH condition the suppression is an average of 0.637±0.020 and 0.406±0.008 z-score below the sustained response, for monkey H and monkey K respectively, while in the LL condition the suppression is an average of 0.487±0.015 and 0.303±0.008 z-score below the sustained response. In monkey H the HL condition caused a large average suppression of 0.674±0.020 z-score while the LH condition caused a lesser suppression of 0.497±0.014 z-score similar to the LL condition. In monkey K both the HL and LH conditions caused similar average suppressions of 0.359±0.011 and 0.389±0.008 z-score respectively.

We performed Wilcoxon rank sum tests on each channel to test if there was a significantly greater suppression for high reward conditions. In 55/58 and 29/31 channels in monkey H and K respectively there was a significantly larger suppression in the HH vs the LL condition. We then tested if there was also a larger suppression for when the nearer saccade target was highly rewarded (HL condition) vs when the further saccade target was highly rewarded (LH condition). In 56/58 and 11/31 channels there was a signif-

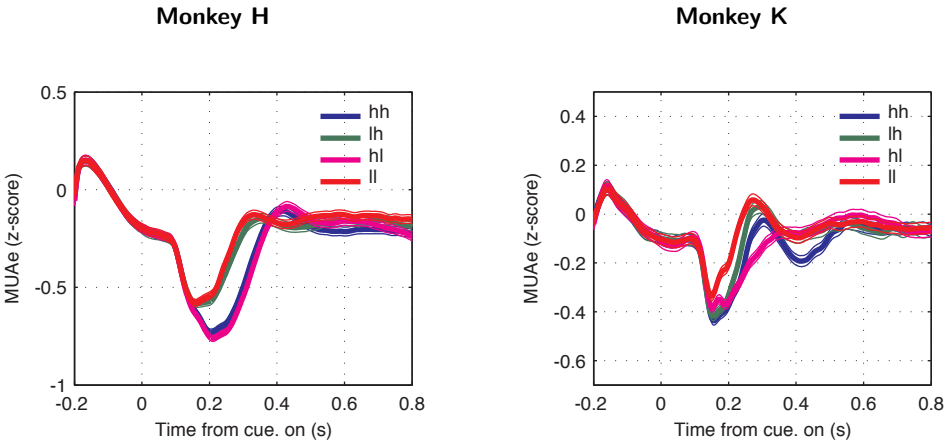

Figure 3.11 | MUAx response to cue onset
When normalized to the pre-cue period it is clear that the suppression in the neural activity is much less for the LL condition in both monkeys as well as the LH condition in Monkey H. The time of maximum suppression also seems to be slightly earlier for the LL and LH conditions. Plot shows the mean and SEM of activity across all included electrodes for each monkey.

icantly larger extent of suppression in the HL vs the LH conditions (see Figure 3.12). This means that for monkey K there was a similar sized suppression no matter where the highly rewarded target was on the screen, near or far. An array plot for each monkey is shown in Figure 3.13 where it is possible to see that almost every channel shows the HH vs LL effect for both monkeys while only monkey H shows a clear HL vs LH effect.

By looking at the single channel plots in Figure 3.13 it is possible to see that the timing of the minimum of the dip seems to be later when there is a suppression caused by high reward compared to when the suppression is caused by low reward. The average time of dip minimum in the HH condition was 207±0.44 and 195±0.46 ms for monkey H and monkey K respectively while for the LL condition the time was 193±0.36 and 191±0.43 ms. We performed a Wilcoxon rank sum test of the time of the dip minimum to see if this difference was significant. In 57/58 and 15/31 channels in monkey H and K respectively there was a significantly later time to reach the minimum in the HH vs the LL condition. We then tested if there was also a later time to reach the minimum for when the nearer saccade target was highly rewarded (HL condition) vs when the further saccade target was highly rewarded (LH condition). The average time of dip minimum in the HL condition was 209±0.45 and 198±0.30 ms for monkey H and

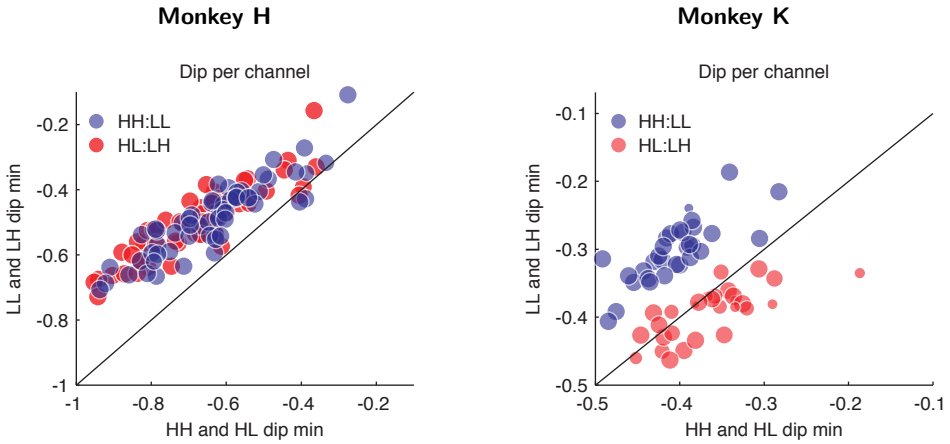

Figure 3.12 | Average MUAx suppression
Note that in monkey H the increase in suppression for HL vs LH is almost identical as HH vs LL. In monkey K all reward conditions show suppression except LL and there is little difference in the suppression for HL vs LH. Each point is one electrode, point size reflects the significance level as shown in Table 2.

monkey K respectively while for the LH condition the time was 196±0.38 and 192±0.47 ms. In 57/58 and 29/31 channels there was a significantly later time of the minimum suppression in the HL vs the LH conditions (see Figure 3.14). While this effect was highly significant for monkey H in monkey K only half the channels showed the effect significantly, although on average the minimum of the suppression for high reward was later than for low reward.

We next looked at whether there was a change in the variability of the firing of the neurons at the time of the cue onset. Previous work has shown that stimulus onset causes a decrease in variability (Churchland et al. 2010), however it is not yet known whether a stimulus onset in the surround of a RF (i.e. our cue) causes a similar decrease. To control for differences in variability due to the observed firing rate decrease at cue onset we followed a mean matching procedure as in (Churchland et al. 2010) (see Methods 3.1). We found that there was little change in the population Fano factor after cue onset, although it did seem to decrease slightly (see Figure 3.15). For the mean matched Fano factor the differences between the conditions during the bin with the maximum suppression (160-240 ms after cue onset) were tested using a Z test. For monkey H there was a change of -0.017±0.010 between the HH and LL conditions which was not significant (p=0.112) and a change of -0.032±0.010 between the HL and

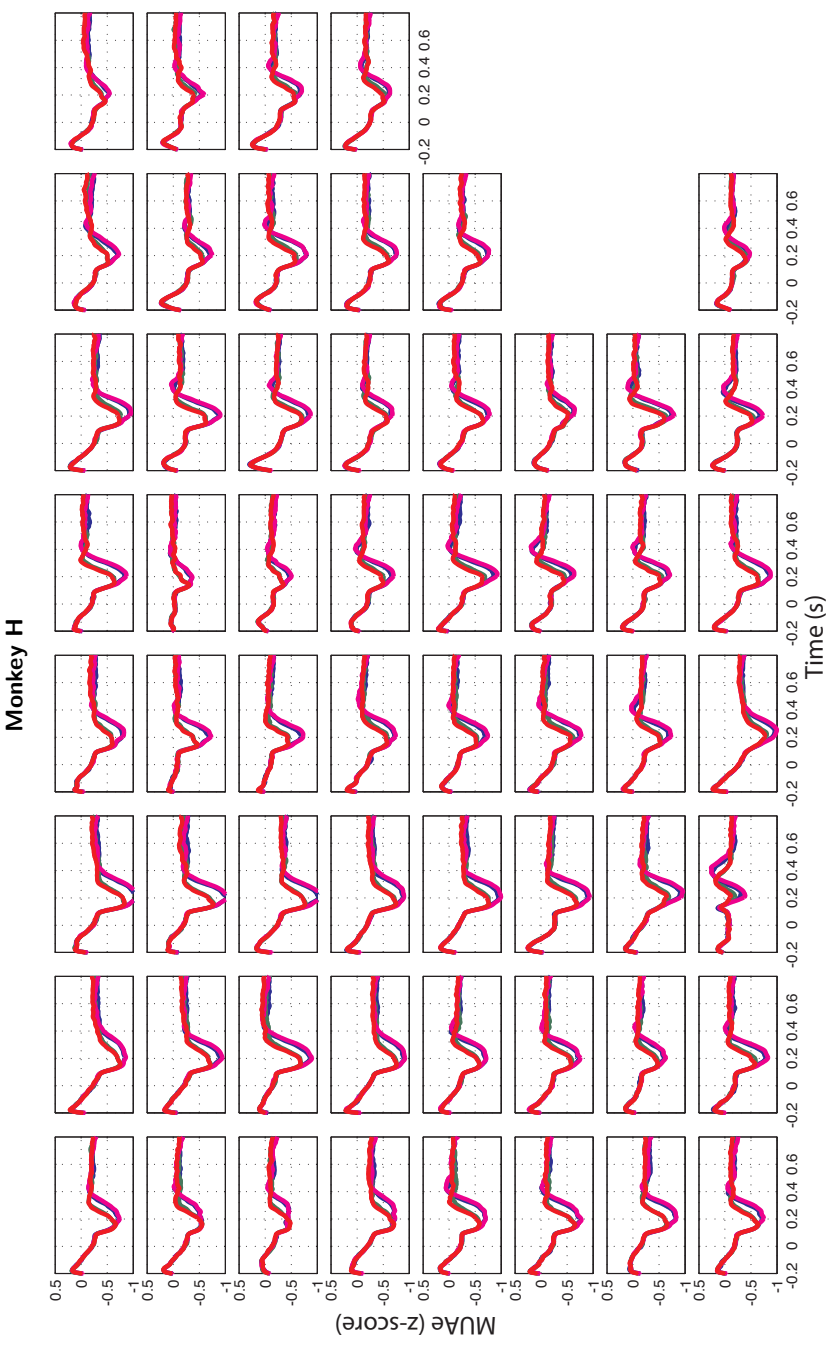

Figure 3.13 | MUAx array response to cue onset
Almost all channels show the effect. These are all the channels used for analysis, they needed a sustained response of 0.3 z-scores above the baseline to be included.
Continued in next panel.

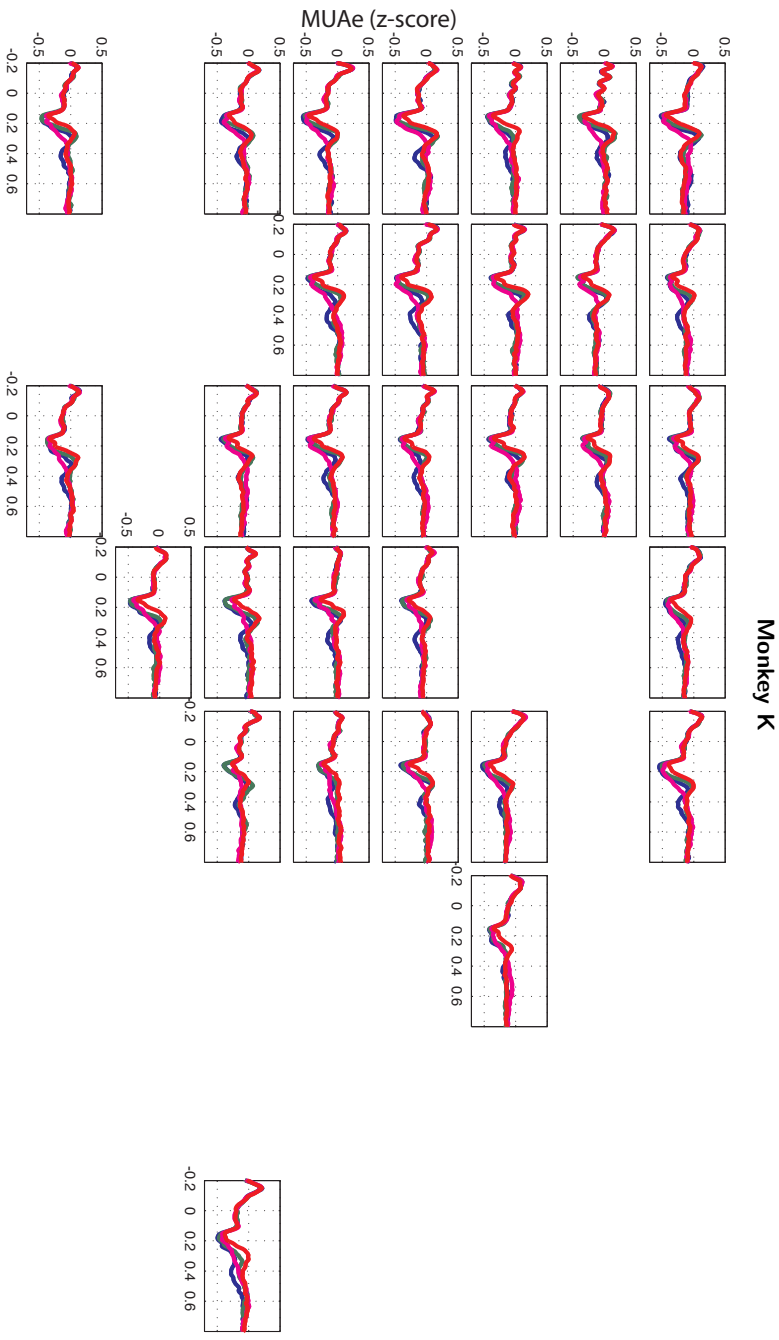

Figure 3.13 | MUAx array response to cue onset
Continued from previous.

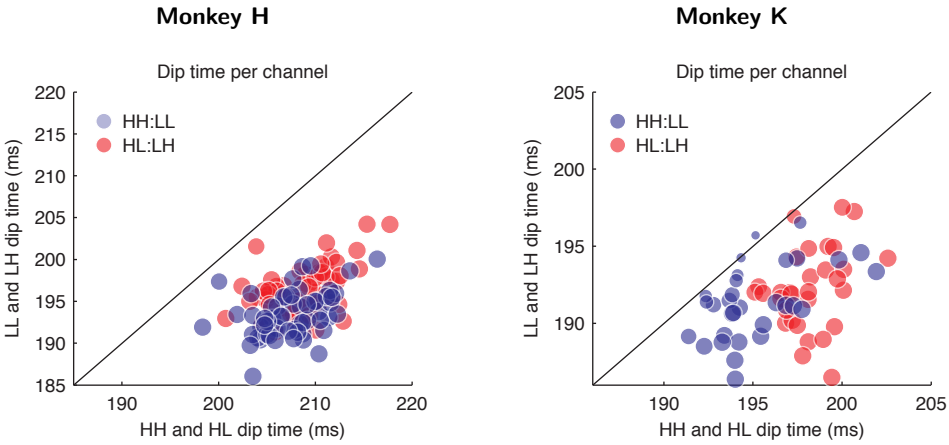

Figure 3.14 | Average time to reach the minimum of MUAx suppression Note that in monkey H the time of maximum suppression for HL vs LH is very similar to HH vs LL. In monkey K both HL vs LH and HH vs LL show a difference in the time to maximum suppression but this difference is less for HH vs LL. Each point is one electrode, point size reflects the significance level as shown in Table 3.

LH conditions which was significant (p=0.013). For monkey K there was a change of -0.042±0.021 between the HH and LL conditions and a change of -0.006±0.020 between the HL and LH conditions neither of which was significant (p=0.078 and p=0.425 respectively). However the Fano factor values for our MUAx are very different to those usually found for spike data so it may be that this result is not applicable to spiking data.

Neural activity throughout the task

First we looked to see if the lower activity with high reward was sustained through later periods of the task. We took only trials with a separation of at least 1.5 s between the onset of the cue and the onset of the motion and analyzed whether the suppression was still present on average between 1 to 1.5 s post cue onset. In monkey H most channels still showed a slight suppression during this period in the HH vs LL condition (58/58 channels were significantly suppressed), although the average difference per channel was only 0.12 z-score (see Figure 3.16). However, in monkey K most channels did not show greater suppression in the high reward condition during this period (6/31 channels were significantly suppressed).

We next investigated the motion period of the task. Since reward biased the selection of the saccade target based on the strength of the motion,

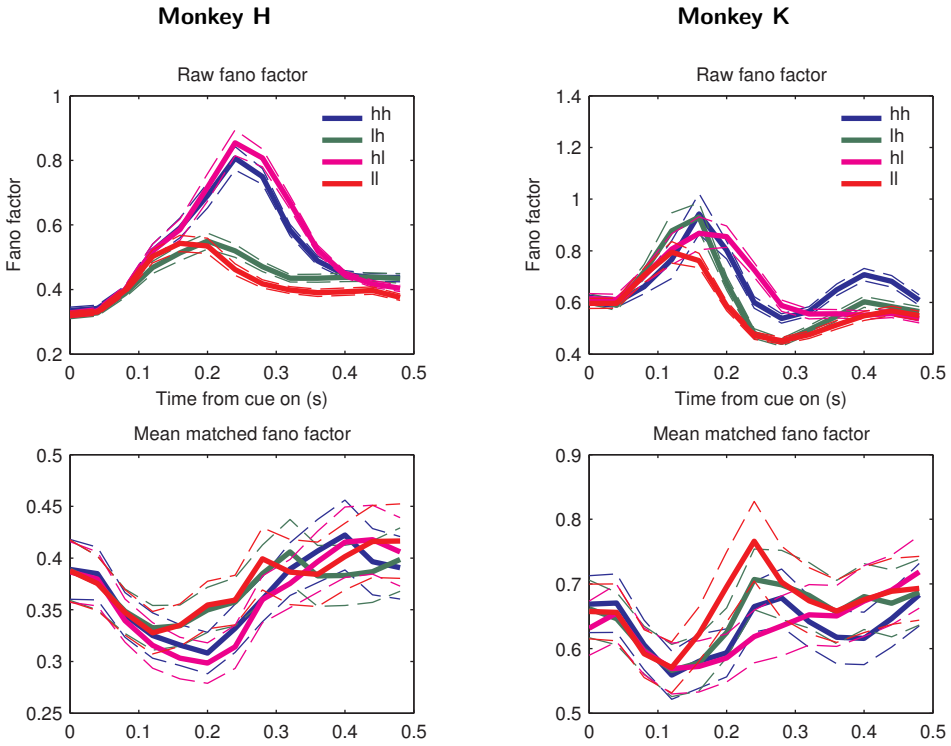

Figure 3.15 | Fano factor at cue onset
The variability seems to decrease at cue onset when using the mean matching procedure but increases in the raw Fano factor. Variability is generally expected to decrease with lower firing rates. As can be seen here is no significant difference between reward conditions in the mean matched Fano factor.

we expected that the reward might change the response to the motion onset. However, this does not appear to be the case. In Figure 3.17 it can be seen that there is a very small increase in the strength of the motion response during a high rewarded vs a low rewarded trial (blue points in Figure 3.18). We performed a Wilcoxon rank sum test and found that for monkey H there were significant increases in the motion response during the HH condition but this was not the case for monkey K. In 52/58 and 18/31 channels in monkey H and K respectively there was a significantly larger upwards motion response in the HH condition vs LL condition and in 57/58 and 0/31 channels there was a significantly larger downwards motion response (see Tables 5 and 6). There was no difference in the upwards or downwards motion strength when only one of the two directions is highly rewarded (red points in Figure 3.18). Responses to upwards motion in the LH vs HL condition were significantly larger in 0/58 and 2/31 channels

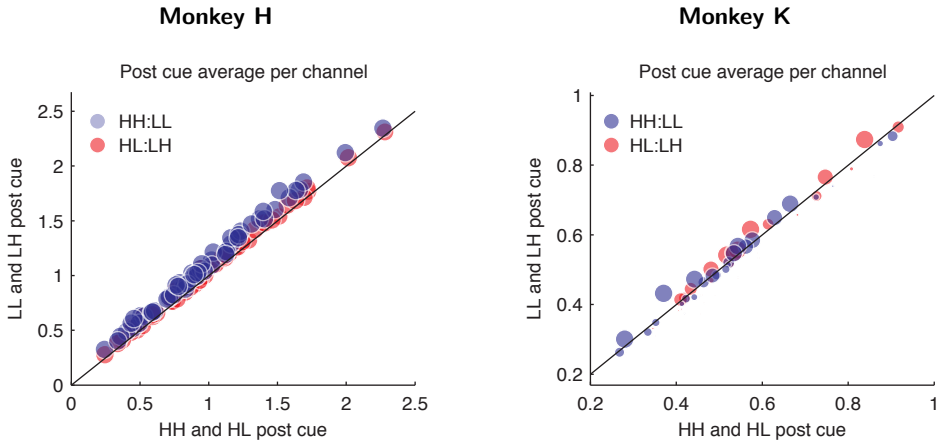

Figure 3.16 | Average MUAx during post cue period
Most channels in monkey H are suppressed but to a very small extent. In monkey K most channels are no longer suppressed. Each point is one electrode, point size reflects the significance level as shown in Table 4.

in monkey H and monkey K respectively, while responses to downwards motion in the HL vs LH condition was significantly larger in only 25/58 and 6/31 channels in monkey H and K respectively (see Tables 5 and 6). This is the opposite to what we expected to see based on feature attention literature (Ibos and Freedman 2016). V4 is not a strongly motion selective area, in previous studies only around 15% of neurons have been found to be motion selective (Desimone and Schein (1987) but see also Tolias et al. (2005)). However, we found motion direction selectivity (i.e. significantly stronger activity for either upwards or downwards motion) in 55/58 and 30/31 of our channels for monkey H and monkey K respectively, so it is still surprising that there was no difference with reward (see Figure 3.19).

We next decided to investigate if we could predict the choice of the monkey at the end of the trial based on the responses of the V4 channels to the motion event (choice probabilities). The median choice probabilities for V4 in each reward condition were 0.53,0.53,0.53 and 0.53 for HH, LH, HL and LL respectively for monkey H and 0.52,0.55,0.53 and 0.52 for monkey K. We tested whether choice probabilities were stronger on trials when the reward values were equal between the two saccade targets (HH and LL) or when they were unequal (HL and LH). We reasoned that, as a visual area, V4 might be better able to predict choice when reward was not biasing the choice of the monkey. And indeed, when tested with a

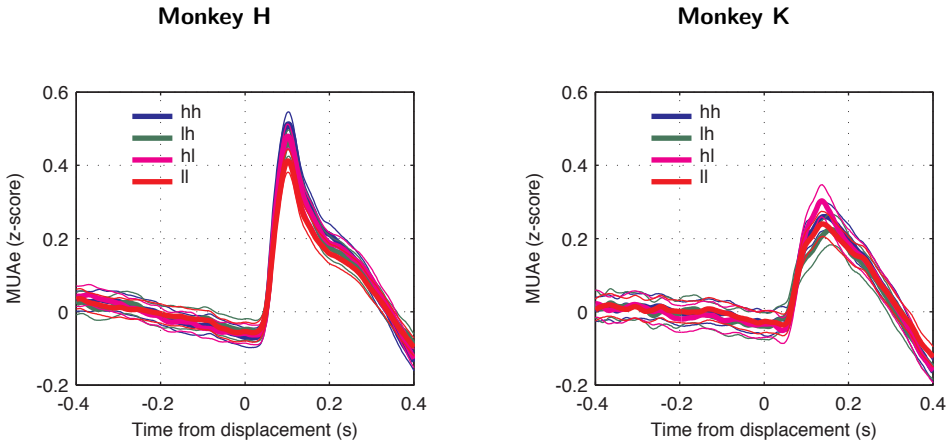

Figure 3.17 | MUAx response to motion onset
Almost no difference in motion response is seen between reward conditions when normalized to the period before the displacement occurs. Motion responses in V4 were weak but clearly present. Plot shows the mean and SEM of activity across all included electrodes for each monkey.

Wilcoxon rank sum test, choice probabilities across electrodes were significantly higher for equal rewards than for unequal rewards (see Figures 3.20 and 3.21, p=0.037(d.f.=114) for monkey H and p=0.004(d.f.=60) for monkey K). Although there were significant differences between the conditions, the effect size was very small (the median increased from 0.522 to 0.537 for monkey H and from 0.508 to 0.513 for monkey K). 39/58 and 13/31 V4 channels in monkey H and monkey K respectively showed significant choice probabilities in the equal conditions while 32/58 and 5/31 V4 channels in monkey H and monkey K respectively showed significant choice probabilities in the unequal conditions (see Table 8).

Previous work has found differences in the responses of visual neurons based on the certainty of the animals that they are correct (Komura et al. 2013). We reasoned that with our paradigm if the monkey saccaded towards a low rewarded target when there was a high rewarded target in the other direction, then they must have been very certain that the motion was in that direction. We call those trials *sure*, while the trials when the monkey was saccading towards the high rewarded target in the presence of a low rewarded targets are called *unsure*. Behaviorally this effect can be seen in the psychometric curve in Figure 3.7. Both monkeys were very rarely wrong when saccading towards the low rewarded target when the high rewarded target was present (90.85% and 98.9% correct trials for monkey

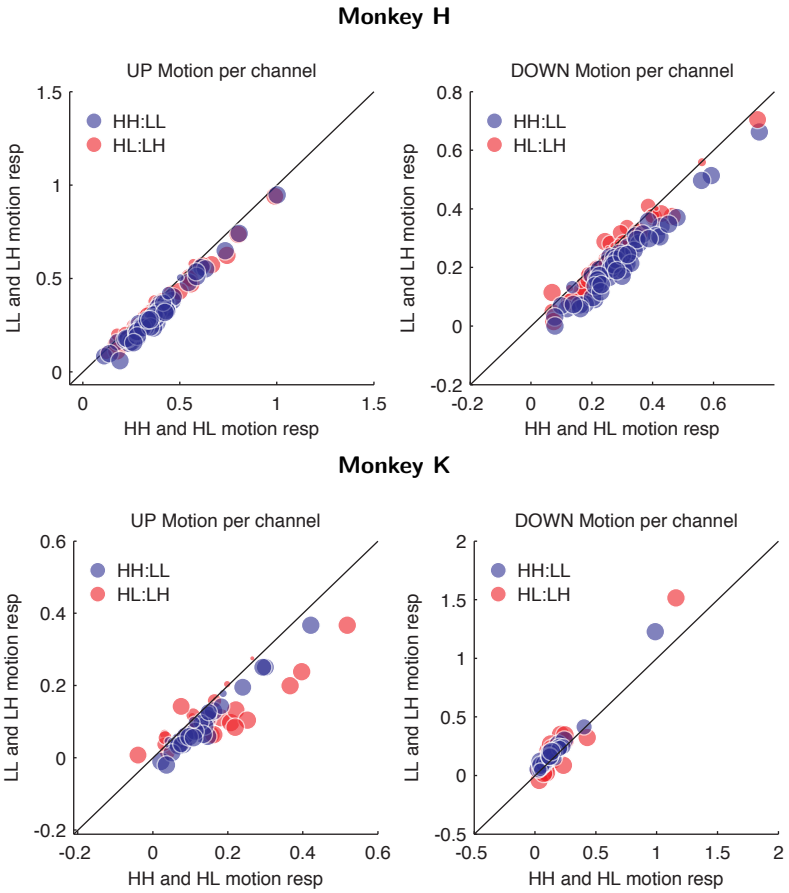

Figure 3.18 | Average MUAx motion response split by direction and reward condition
Motion response to both directions split by reward condition. LH is high reward for upwards motion, HL is high reward for downwards motion. Each point is one electrode, point size reflects the significance level as shown for upwards motion in Table 5 and downwards motion in Table 6.

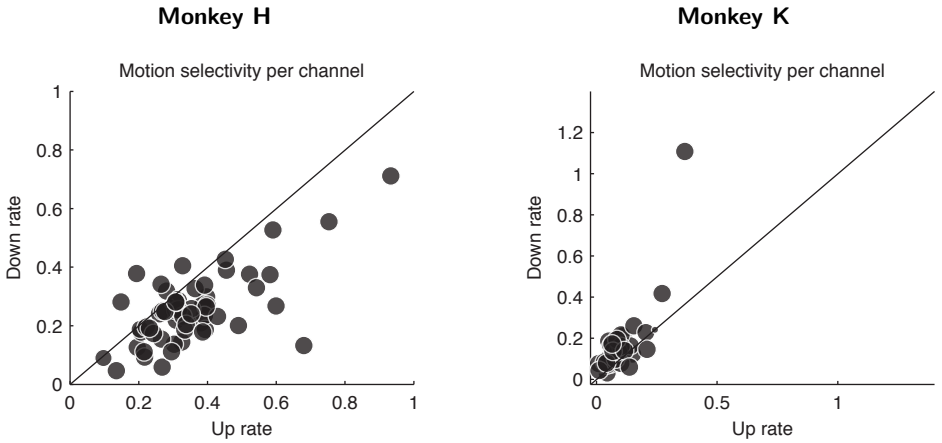

Figure 3.19 | Average MUAx motion selectivity
Most channels are significantly motion selective in both monkeys. Each point is one electrode, point size reflects the significance level as shown in Table 7.

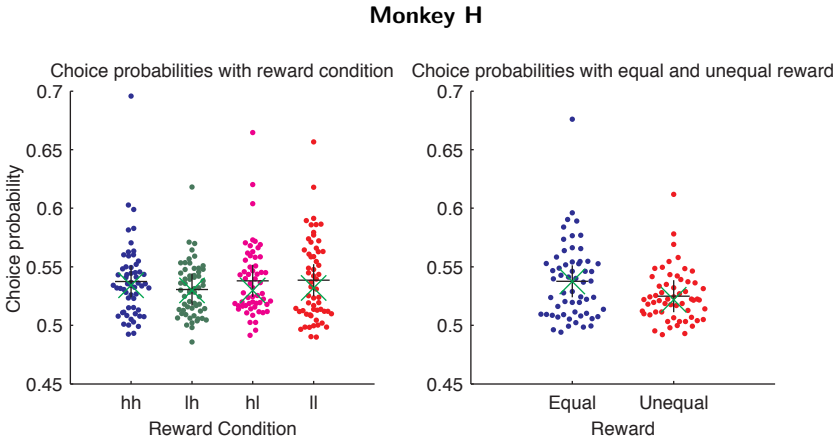

Figure 3.20 | Choice probabilities for each channel
Choice probabilities split into conditions and into equal and unequal reward. A green X signifies the median and a black + is the mean. When split into equal and unequal reward conditions a small but significant effect is seen in choice probabilities in the equal reward condition.
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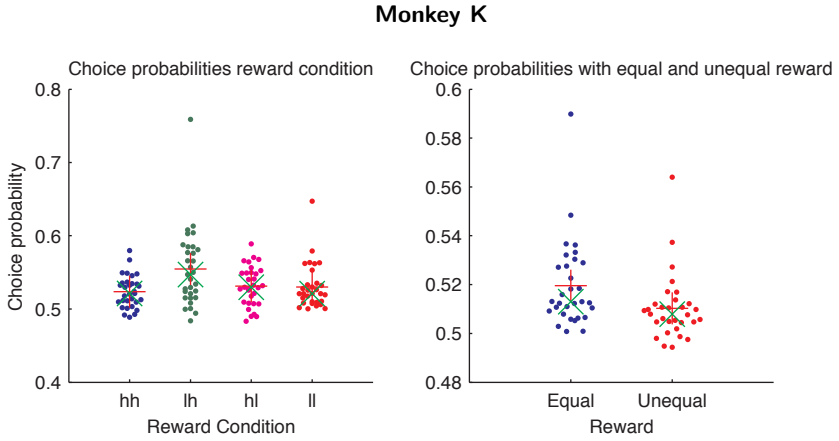

Figure 3.20 | Choice probabilities for each channel
Continued from previous. Again for monkey K there is a small but significant increase in choice probabilities in the equal reward condition compared to the unequal reward condition.

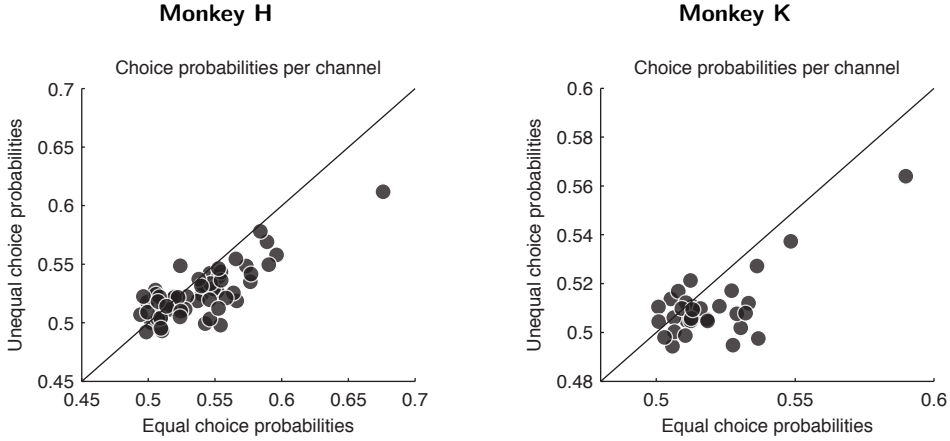

Figure 3.21 | Choice probabilities for each channel
Scatter plot showing the same data as 3.20. There is an increase in choice probabilities in the equal reward condition for most channels.

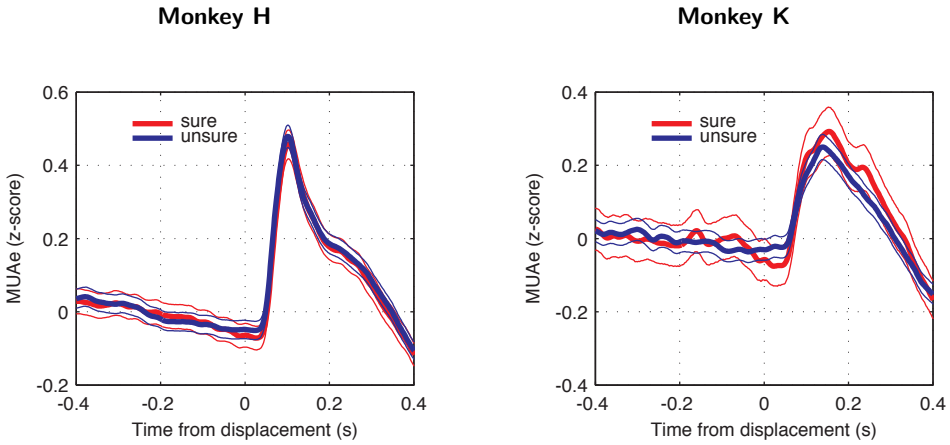

Figure 3.22 | MUAx certainty response to motion onset
When split by sure vs unsure trials very little difference is seen in the motion response. A slight increase in response may be present in monkey K. Plot shows the average mean and SEM of across all included electrodes for each monkey.

H and K respectively), but were often wrong when saccading towards the high rewarded target when the other target was low rewarded (50.36% and 26.6% correct trials for monkey H and K respectively).

However, neurally there was again no consistent difference between the motion response for sure and unsure trials (see Figure 3.22). For the sure trials the average motion response was 0.601±0.030 and 0.456±0.046 z-score for monkey H and monkey K respectively, and for unsure trials the average motion response was similar, 0.614±0.030 and 0.353±0.046 z-score. This was tested using a Wilcoxon rank sum test, in monkey K it seems that there might be a slightly stronger motion response on sure trials (11/31 significant V4 channels) but for monkey H there is no difference (8/58 significant V4 channels) (see Table 9).

Based on the Baruni, Lau, and Salzman (2015) paper and the Ghosh and Maunsell (2016) abstract we found it very surprising that we did not see sustained differences in the firing of V4 neurons with reward (as discussed in the introduction Section 1.3). We wondered if this was due to the fact that in their paradigms the monkey already knew the reward amounts before stimulus onset and peak normalization was performed as baselining. We ran one session in monkey K in which the colored saccade targets came on *before* the stimulus onset and we peak normalized to this stimulus onset for each channel. As before, during the cue period we saw suppression but

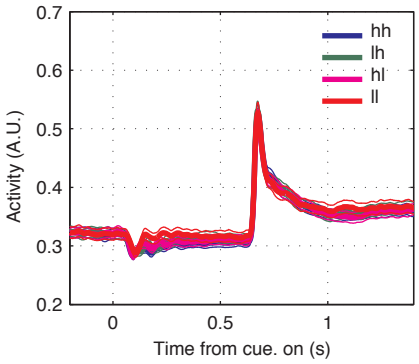

Figure 3.23 | Cue period before stimulus onset
Neural suppression is seen as in the previous task but to a much lesser extent. This plot uses peak normalization as Baruni, Lau, and Salzman (2015). Note that this plot comes from only one session of data. Plot shows the average activity across all included electrodes.

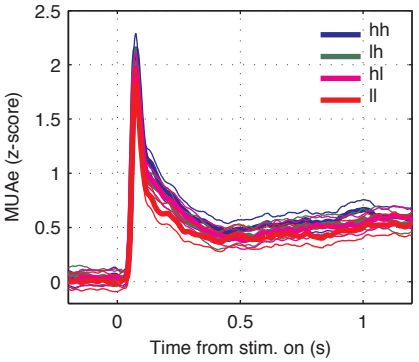

Figure 3.24 | Stimulus onset when cue is present
When normalized to the cue period the stimulus onset period shows a sustained increase in firing for HH vs LL. Note that this plot comes from only one session of data. Plot shows the average activity across all included electrodes.

it was overall much weaker, perhaps due to the lower firing rates without a stimulus on screen (see Figure 3.23). However, during the stimulus onset we saw very little difference between the conditions. If anything, the LL condition showed a slight increase in this case (55/56 channels had greater sustained responses to LL than HH), which is the opposite to the effect seen in Baruni, Lau, and Salzman (2015). However, if we baselined the stimulus onset to the cue period we saw results that look extremely similar to the Baruni, Lau, and Salzman (2015) and Ghosh and Maunsell (2016) reward effects (see Figure 3.24). Behavioral results from this session show that the monkey was biased in the LH and HL conditions as expected.

3.3 Discussion

Here we have found surprising effects of reward on the firing of V4 neurons. Based on previous work we would have expected that during high reward conditions V4 neurons would fire more and during low reward conditions V4 neurons would fire less (Baruni, Lau, and Salzman 2015; Ghosh and Maunsell 2016) (see Section 1.3). However, instead we found that after the onset of the reward cue a large suppression in the firing of the V4 neurons takes place, and that this suppression is larger for higher reward (see Figure 3.11). Suppression appears to only occur if the reward cue is in the suppressive surround of the neuron. After this brief suppression period the activity of neurons returns to equivalent levels and is almost no longer reward dependent (see Figure 3.16). This result may align with an fMRI study by Arsenault et al. (2013) which found that after a reward, negative BOLD increases, previously shown to be associated with surround suppression (see Section 1.3, and Shmuel et al. (2006)). While the neural signal was dependent on the value of targets in the suppressive surround, the pupil signal was dependent on the expected reward of the trial (Figure 3.9). Here we try to clarify why we have found such different results to the previous literature.

As explored in the introduction Section 1.3 one previous study has investigated the effects of reward on the firing of V4 neurons (Baruni, Lau, and Salzman 2015). Unlike our task, reward cues were presented before the onset of the stimulus and turned off before stimulus onset. Baruni, Lau, and Salzman (2015) found a sustained increase in firing in response to stimuli with a high reward value from around 300 ms after stimulus onset. If any suppression was present in response to their cue onset they do not report it. But since they use a peak normalizing procedure it may be that suppression is less obvious. One of their example neurons may show a slight suppression before the stimulus onset and after the cue offset, using non-baselined spike counts, but the other neurons show no such effect (see Figure 1.11). However, it is difficult to observe suppression with a baseline firing rate of around 5 spikes per second. Because our stimulus was already on at the time of the cue, we have a strong firing rate to suppress. Additionally we are using MUAx signals instead of spike counts which pick up the activity of many neurons and therefore may be more sensitive for population changes.

We attempted to replicate exactly the results of Baruni, Lau, and Salzman (2015) by turning the cue off before the onset of the visual stimulus. How-

ever, in training trials we found that the monkey showed no bias towards the high reward direction, indicating that he was not able to remember the value of the saccade target throughout the rest of the trial. Due to time constraints we could not further investigate why this did not work with our paradigm. This means that although our cue first paradigm is similar to the one used by Baruni, Lau, and Salzman (2015) it is not identical, which could explain why we still don't see the same results that they found in their study.

When using peak normalization as in Baruni, Lau, and Salzman (2015) we did not find the same sustained increase for the HH vs LL condition (high vs low reward), see Figure 3.23. However, when we normalized to the baseline (during the period of suppression) one sees something that looks very much like a sustained enhancement (see Figure 3.24), similar to that found in their paper. This is only due to the baselining procedure making the HH and LL equivalent before stimulus onset, which is adding to the HH signal due to the large suppression and subtracting from the LL signal due to the smaller suppression.

We have unexpectedly found very little difference in the activity of V4 neurons in the entire rest of the task time after the cue onset. This could be at least partially due to the paradigm we chose to explore this question with. In our task the small displacement of the grating (making an apparent motion stimulus) was the information on which the monkey had to base their choice of saccade target. We did not see any consistent change in the responses of the V4 neurons to this motion no matter what type of reward trial it was. However, as shown earlier in Figure 3.17, the V4 neurons did not respond particularly strongly to the motion.

It is known that area MT is one of the first areas in the visual hierarchy that is sensitive to apparent motion (Newsome, Mikami, and Wurtz 1986). V4 is not a very motion responsive area (Desimone and Schein 1987), and is in fact part of the ventral stream which is selective for object recognition rather than object speed or location (see Figure 1.3). We cannot rule out that if we had instead used a classical paradigm, for example orientation discrimination, we might have seen very different results.

As mentioned in the introduction section 1.3 one previous paper has found effects of attention on the extent of surround suppression (Sundberg, Mitchell, and Reynolds 2009). This could be similar to what we have found here in that it is likely that the monkeys would pay attention to the cue at the time

of onset. The suppression would be caused initially by exogenous attention as the abrupt onset of the color change acts as a exogenous cue. Then it could be that the color indicating the high reward somehow attracts the endogenous attention of the monkey causing an increase in the amount of suppression for high value cues. Although there has not been very much research into the effects of attention on the extent of surround suppression, it has been known for many years the ability to attend selectively to something is dependent on the ability to suppress other inputs. Attention effects in V4 are far more clear when there are two stimuli within the RF rather than just one (Moran and Desimone 1985). When two stimuli are in the RF of a V4 neuron the neuron responds as though only the attended one is present, almost completely suppressing its response to the unattended stimulus. Additionally the strongest indication of attention is found in the increase of alpha power (thought to be involved in cortical suppression (for review see Foxe and A. C. Snyder (2011))) over the unattended stimuli rather than the enhancement of gamma over the attended one. This can be related to the idea of "limited bandwidth", that we are only able to completely process a small amount of, for example, the visual scene at one time, and suppression ensures that only relevant signals are passed onto higher areas for further processing.

While previous research on attention could explain the results we have found, as discussed in the introduction section 1.3 in most attention studies it is impossible to parse apart the effects of reward and attention. Previous research on reward could also give insight into what is happening in our results. Unexpected reward causes a release of neurotransmitters, for example dopamine, which have been shown to have effects on learning (Arsenault et al. 2013), memory (White and Viaud 1991) and synaptic efficacy (Frey, Schroeder, and Matthies 1990) (see Section 1.3). One study in particular has shown changes in the orientation sensitivity of humans due to reward without conscious awareness let alone attention (Seitz, D. Kim, and Watanabe 2009). This took place without any kind of task with only the pairing of reward and a particular orientation, mimicking a classical conditioning paradigm. Eye specificity of the effect demonstrates that this is taking place at very early stages of visual processing. This strengthening of representations of stimuli associated with reward is completely unconscious and it can take place at the expense of task performance (Anderson, Kuwabara, et al. 2016) even after periods of up to 6 months (Anderson and Yantis 2013). While ultimately there are multiple possible interpretations of our results, we have shown that reward values of stimuli are certainly reflected in the firing rates of neurons in V4.

Chapter 4

Conclusion

4.1 The role of noise correlations in V4

In chapter 2, Noise Correlations, we have shown that noise correlations in V4 stay the same or slightly increase after a V1 lesion, which removed the cascade of feedforward input to V4. This was true across multiple timescales as well as across the spatial scale. This signifies that noise correlations are likely to be due to feedback or recurrent connections between neurons, and this conclusion has also been backed up by previous electrophysiological and theoretical lines of research (Smith and Kohn 2008; Smith and Sommer 2013; Rosenbaum et al. 2016). If this is indeed the case, then noise correlations are internally generated by the brain and are not an unavoidable part of shared inputs from noisy sensory organs as was originally thought (Zohary, Shadlen, and Newsome 1994). As explored in the introduction, section 1.2, they can be harmful for decoding the sensory stimulus. This begs the question of why the brain is generating these correlations.

Noise correlation, or correlated neuronal variability, is calculated by subtracting the mean response from the trial by trial fluctuations of responses to identical stimuli and then correlating these fluctuations between pairs of neurons. This assumes that all the relevant "signal" is found in the pre-

sented stimulus and all other fluctuations are due to "noise". However, it is likely that there is information that is highly relevant to (in this case) the visual cortex that is not contained in the presented stimulus. The brain is not just encoding visual stimuli but has a multitude of other functions as well. One possible source of the "noise" could be reward information. As explored in the introduction section 1.3 and in chapter 3 reward related activity is relayed throughout the brain through the activity of dopaminergic neurons (Arsenault et al. 2013). This could have long lasting effects on information processing and would be included in the "noise" component as it is often not under tight experimental control. It seems that the dopaminergic neurons in the lateral ventral tegmental area (VTA) have extremely high noise correlations, particularly interesting because of their very low firing rates which generally lowers noise correlations (Eshel et al. 2016; Y. Kim, J. Wood, and Moghaddam 2012). Another source of "noise" could be multimodal integration. It has been shown that V1 receives direct input from auditory cortex and there are many auditory related visual illusions in which the presentation of double beeps induce the percept of a double flash visual stimulus when in reality only a single stimulus was shown. This is obviously important information for the brain but could easily vary from trial to trial when only the visual stimulus is being controlled.

A final possibility is that noise is not as harmful to coding as is often assumed in theoretical studies. Many experimental studies have shown that attention causes a decrease in noise correlations, which may be stronger than attention associated changes in firing rate (Cohen and Maunsell 2009; Baruni, Lau, and Salzman 2015). One study by Ruff and Cohen (2014) tried to investigate if this was always the case or if attentional engagement only decreased noise correlations when this was useful for the task. When pairs of neurons with similar tunings are engaged in discriminating stimuli then noise correlations are harmful, and they found that between these pairs noise correlations are decreased with attention. However, if the pair have dissimilar tuning then noise correlations can be beneficial to discriminate stimuli, and Ruff and Cohen (2014) found that in these pairs the noise correlations were instead increased. As (seemingly) noise correlations can be enhanced or reduced by feedback activity depending on their use in a task it may be that they are specifically present when necessary for computations and that we have not yet understood some of their potential functions for information coding. Taking the above information into account, chapter 2 has provided a very interesting finding that may help to elucidate the function of noise correlations in the brain. However, there are many further questions that remained to be answered.

4.2 The role of reward in V4

In chapter 3, Reward Related Activity, it was shown that the onset of a highly rewarded saccade target causes stronger surround suppression in visual area V4 than one that is less highly rewarded. Although the reward caused strong behavioral biases in both monkeys, as well as differences in the pupil response, I found very few differences in neuronal firing to any portion of the task except the cue onset. While there are many possible reasons that this may be the case, as explored throughout the discussion, it seems most likely that reward activates a general mechanism propagating throughout the cortex to highlight possible links between rewards and stimuli that have recently been perceived. For the mechanism to be useful for reward based learning and reflect the findings here it would have to have some specific features. Stimuli that are linked to high reward through this mechanism would have to become more easily detected in future, potentially through increased surround suppression. This in turn would result in the brain reacting by increasing the "salience" of reward related stimuli. As shown in chapter 3, the hypothesized mechanism would have to cause changes in neuronal responses but these must be flexible so that they can be switched within a few hundred trials. The mechanism must also be specific to particular behavioral contexts, time sensitive and present across modalities.

What might this mechanism to cause reward related activity changes be? As discussed in the introduction (Section 1.3, dopaminergic neurons have previously been shown increase their firing to unexpected reward and project throughout the cortex. This increase of firing is specific to unexpected reward and a decrease is found instead if an expected reward does not take place (Hollerman and Schultz 1998). Blocking of dopamine receptors can impair certain reward cue learning paradigms (Flagel et al. 2011) and both the context and the timing of reward affects the firing of dopaminergic neurons (Kobayashi and Schultz 2008). While the later phase of a dopamine response seems proportional to the amount of expected reward, the earliest part of the response seems to correlate with the strength of the stimulus (from any modality), i.e. its salience (Schultz 2016). This makes dopamine signaling a perfect candidate to both represent the salience of stimuli across the rest of the brain, allow the learning of new reward/stimulus pairings and additionally increase behavioral responses towards these stimuli.

Here I have shown that surround suppression seems to be involved in the representation of reward in the visual cortex. Two previous studies have

found attention or reward related effects on neuronal surround suppression. Sundberg, Mitchell, and Reynolds (2009) investigated extent of the suppression of responses of V4 neurons to gratings presented in the center of their RFs when an attended (i.e. rewarded) stimulus was presented in the surround as opposed to an unattended stimulus. Having an attended stimulus in the surround increased the extent of surround suppression from an 11.6% decrease to a 17.7% change. Additionally, when the stimulus in the center of the RF was rewarded while the stimulus in the surround was unrewarded, the responses of the neuron within the receptive field were almost the same as when there was nothing presented in the surround (5.3% change). Verhoef and Maunsell (2016) systematically investigated receptive field properties of V4 neurons and the effect of attention (i.e. likelihood of reward) on their responses. They found that the extent of the change in firing due to attention was a combination of the amount of excitatory drive provided by the attended/rewarded stimulus and the amount of suppressive drive provided by the unattended/unrewarded stimulus. This was not specific to surround stimulus' placement in the surround of the receptive field but also varied with its orientation and other stimulus features. I found similar effects, in one monkey the upper saccade target caused no suppression effect at all, likely because it was too far outside the receptive field to cause any suppression, and (not shown) that the extent of the suppression due to green saccade targets was less than blue saccade targets which in turn affected the size of the reward related suppression.

Taking all these previous studies into account, what might be happening in our results? In the context of the reward paradigm examined here we must keep in mind that area V4 is far more selective for the color of stimuli than their motion direction (Roe et al. 2012). When the colored saccade targets turned on, dopaminergic neurons sensitive to reward values may have been responding to the level of reward predicted by the condition based on the learned reward/color association. This phase of the dopamenergic firing is over after ∼400 ms (Schultz 2016). I would argue based on the results in chapter 3 that this, directly or indirectly via feedback from higher areas, causes a suppressive effect on all V4 neurons that do not have the stimulus in the center of their RF so that the most rewarded stimuli are those best represented by V4. This effect happened most strongly when an excitatory stimulus was in the center of their receptive field but also took place in the cue first session without a stimulus present but to a lesser extent (see Figure 3.23, similar to Verhoef and Maunsell (2016)). Since V4 is not particularly motion selective and there is no competing salient stimulus I observed very little reward related change in response to the motion. Had we recorded

in a motion selective area (like MT) or used multiple competing stimuli I may have seen reward related effects in this period of the task.

This project has opened up many interesting questions on the effects of reward on activity in visual area V4. One obvious next step would be to use discriminada that were well represented by area V4, i.e. use a similar discrimination task but have the event be an orientation or color change and see if this caused any changes in the representation of the stimuli with high reward. Another step would be to use multiple competing stimuli in order to better engage surround suppression mechanisms and see if this caused a change in activity with reward similar to that seen by Baruni, Lau, and Salzman (2015) and Ghosh and Maunsell (2016). Inactivating V4 during the performance of the task would show whether activity in V4 was necessary to correctly perform the task (based on previous literature with our paradigm this would be unlikely to have been the case (Desimone and Schein 1987)) and how much the activity of early cortical areas influences the choice of the monkey in a biased discrimination task as was suggested by significant choice probabilities in some neurons. Overall, I have found a mechanism through which reward information is processed in the cortex but further experiments will be necessary to understand it in more depth.

4.3 Closing remarks

The findings presented in chapters 2 and 3 have added to our understanding of the mechanisms at work in visual area V4. Traditionally V4 has been viewed as a color responsive area with a role in object feature detection and attention. Based on the results of this thesis I suggest that V4 is a brain area that is not only involved in the basic encoding of features of visual stimuli but also in the representation of internally generated information. This was shown in the maintenance of noise correlations in V4 without sensory input and by the coding of reward information through increased surround suppression. The representation of reward information at this level may be particularly important in allowing the visual system to preferentially encode high value stimuli. These mechanisms are vital to understand how the brain can create stable perceptions of the world, how it can effortlessly learn to recognize important new objects and how it can interact with the outside world.

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Appendix

Acronyms

BOLD blood-oxygen-level dependent. 15

DRES Dopamine Reward Error Signaling. 16

ESP excitatory synaptic potential. 39

fMRI functional magnetic resonance imaging. 6

LGN lateral geniculate nucleus. 4

PSTH peri stimulus time histogram. 11

RDK random dot kinematogram. 18

RF receptive field. 6–10, 18, 19

SC superior colliculus. 4

TCC trial cross-covariance. 32

VTA ventral tegmental area. 72

Monkey H

	HH	LH	HL	LL
V4-1	0.0000	0.0000	0.0000	0.0000
V4-2	0.0000	0.0000	0.0000	0.0000
V4-3	0.0000	0.0000	0.0000	0.0000
V4-4	0.0000	0.0000	0.0000	0.0000
V4-5	0.0000	0.0000	0.0000	0.0000
V4-6	0.0000	0.0000	0.0000	0.0000
V4-7	0.0000	0.0000	0.0000	0.0000
V4-8	0.0000	0.0000	0.0000	0.0000
V4-9	0.0000	0.0000	0.0000	0.0000
V4-10	0.0000	0.0000	0.0000	0.0000
V4-11	0.0000	0.0000	0.0000	0.0000
V4-12	0.0000	0.0000	0.0000	0.0000
V4-13	0.0000	0.0000	0.0000	0.0000
V4-14	0.0000	0.0000	0.0000	0.0000
V4-15	0.0000	0.0000	0.0000	0.0000
V4-16	0.0000	0.0000	0.0000	0.0000
V4-17	0.0000	0.0000	0.0000	0.0000
V4-18	0.0000	0.0000	0.0000	0.0000
V4-19	0.0000	0.0000	0.0000	0.0000
V4-20	0.0000	0.0000	0.0000	0.0000
V4-21	0.0000	0.0000	0.0000	0.0000
V4-22	0.0000	0.0000	0.0000	0.0000
V4-23	0.0000	0.0000	0.0000	0.0000
V4-24	0.0000	0.0000	0.0000	0.0000
V4-25	0.0000	0.0000	0.0000	0.0000
V4-26	0.0000	0.0000	0.0000	0.0000
V4-27	0.0000	0.0000	0.0000	0.0000
V4-28	0.0000	0.0000	0.0000	0.0000
V4-29	0.0000	0.0000	0.0000	0.0000
V4-30	0.0000	0.0000	0.0000	0.0000
V4-31	0.0000	0.0000	0.0000	0.0000
V4-32	0.0000	0.0000	0.0000	0.0000
V4-33	0.0000	0.0000	0.0000	0.0000
V4-34	0.0000	0.0000	0.0000	0.0000
V4-35	0.0000	0.0000	0.0000	0.0000
V4-36	0.0000	0.0000	0.0000	0.0000
V4-37	0.0000	0.0000	0.0000	0.0000
V4-38	0.0000	0.0000	0.0000	0.0000
V4-39	0.0000	0.0000	0.0000	0.0000
V4-40	0.0000	0.0000	0.0000	0.0000
V4-41	0.0000	0.0000	0.0000	0.0000
V4-42	0.0000	0.0000	0.0000	0.0000
V4-43	0.0000	0.0000	0.0000	0.0000
V4-44	0.0000	0.0000	0.0000	0.0000
V4-45	0.0000	0.0000	0.0000	0.0000
V4-46	0.0000	0.0000	0.0000	0.0000
V4-47	0.0000	0.0000	0.0000	0.0000
V4-48	0.0000	0.0000	0.0000	0.0000
V4-49	0.0000	0.0000	0.0000	0.0000
V4-50	0.0000	0.0000	0.0000	0.0000
V4-51	0.0000	0.0000	0.0000	0.0000
V4-52	0.0000	0.0000	0.0000	0.0000
V4-53	0.0000	0.0000	0.0000	0.0000
V4-56	0.0000	0.0000	0.0000	0.0000
V4-57	0.0000	0.0000	0.0000	0.0000
V4-58	0.0000	0.0000	0.0000	0.0000
V4-59	0.0000	0.0000	0.0000	0.0000
V4-60	0.0000	0.0000	0.0000	0.0000

Monkey K

	HH	LH	HL	LL
V4-64	0.0000	0.0000	0.0000	0.0000
V4-65	0.0000	0.0000	0.0000	0.0000
V4-66	0.0000	0.0000	0.0000	0.0000
V4-67	0.0000	0.0000	0.0000	0.0000
V4-68	0.0000	0.0000	0.0000	0.0000
V4-69	0.0000	0.0000	0.0000	0.0000
V4-71	0.0000	0.0000	0.0000	0.0000
V4-72	0.0000	0.0000	0.0000	0.0000
V4-73	0.0000	0.0000	0.0000	0.0000
V4-74	0.0000	0.0000	0.0000	0.0000
V4-75	0.0000	0.0000	0.0000	0.0000
V4-76	0.0000	0.0000	0.0000	0.0000
V4-80	0.0000	0.0000	0.0000	0.0000
V4-81	0.0000	0.0000	0.0000	0.0000
V4-82	0.0000	0.0000	0.0000	0.0000
V4-83	0.0000	0.0000	0.0000	0.0000
V4-84	0.0000	0.0000	0.0000	0.0000
V4-85	0.0000	0.0000	0.0000	0.0000
V4-87	0.0000	0.0000	0.0000	0.0000
V4-88	0.0000	0.0000	0.0000	0.0000
V4-91	0.0000	0.0000	0.0000	0.0000
V4-92	0.0000	0.0000	0.0000	0.0000
V4-93	0.0000	0.0000	0.0000	0.0000
V4-94	0.0000	0.0000	0.0000	0.0000
V4-96	0.0000	0.0000	0.0000	0.0000
V4-98	0.0000	0.0000	0.0000	0.0000
V4-99	0.0000	0.0000	0.0000	0.0000
V4-100	0.0000	0.0000	0.0000	0.0000
V4-101	0.0000	0.0000	0.0000	0.0000
V4-106	0.0000	0.0000	0.0000	0.0000
V4-125	0.0000	0.0000	0.0000	0.0000

Table 1 | Significance of suppression
P values for Wilcoxon signed rank tests performed on each channel muax suppression compared to baseline.

Monkey H

	HH vs LL	HL vs LH
V4-1	0.0000	0.0000
V4-2	0.0029	0.0000
V4-3	0.0001	0.0327
V4-4	0.0000	0.0005
V4-5	0.0000	0.0000
V4-6	0.0001	0.0008
V4-7	0.0000	0.0000
V4-8	0.0000	0.0000
V4-9	0.0000	0.0007
V4-10	0.1367	0.0000
V4-11	0.0008	0.0000
V4-12	0.0000	0.0000
V4-13	0.0000	0.0000
V4-14	0.0000	0.0000
V4-15	0.0000	0.0000
V4-16	0.0000	0.0000
V4-17	0.0000	0.0000
V4-18	0.0000	0.0000
V4-19	0.0000	0.0000
V4-20	0.0000	0.0000
V4-21	0.0000	0.0000
V4-22	0.0000	0.0000
V4-23	0.0000	0.0000
V4-24	0.0000	0.0000
V4-25	0.0000	0.0000
V4-26	0.0000	0.0000
V4-27	0.0000	0.0000
V4-28	0.0000	0.0000
V4-29	0.0000	0.0000
V4-30	0.0000	0.0000
V4-31	0.0000	0.0000
V4-32	0.0000	0.0000
V4-33	0.0000	0.0000
V4-34	0.0882	0.0000
V4-35	0.0000	0.0000
V4-36	0.0000	0.0000
V4-37	0.0000	0.0000
V4-38	0.0000	0.0000
V4-39	0.0000	0.0000
V4-40	0.0000	0.0000
V4-41	0.0000	0.0000
V4-42	0.0000	0.0000
V4-43	0.0000	0.0000
V4-44	0.0000	0.0000
V4-45	0.0000	0.0026
V4-46	0.0000	0.1300
V4-47	0.0000	0.0000
V4-48	0.0000	0.0000
V4-49	0.0000	0.0000
V4-50	0.0000	0.0000
V4-51	0.0005	0.0030
V4-52	0.0003	0.0000
V4-53	0.0012	0.0000
V4-56	0.1825	0.9999
V4-57	0.0007	0.0000
V4-58	0.0000	0.0000
V4-59	0.0000	0.0000
V4-60	0.0000	0.0000

Monkey K

	HH vs LL	HL vs LH
V4-64	0.0074	0.4546
V4-65	0.0213	0.2970
V4-66	0.0000	0.0365
V4-67	0.0000	0.0000
V4-68	0.0000	0.0000
V4-69	0.0000	0.2328
V4-71	0.0000	0.0589
V4-72	0.0238	0.9999
V4-73	0.0513	0.3187
V4-74	0.0003	0.0062
V4-75	0.0000	0.0609
V4-76	0.0001	0.1859
V4-80	0.0000	0.0000
V4-81	0.0000	0.2352
V4-82	0.0000	0.2923
V4-83	0.0000	0.8030
V4-84	0.0113	0.0003
V4-85	0.0001	0.0438
V4-87	0.0000	0.0076
V4-88	0.0006	0.0826
V4-91	0.0000	0.1092
V4-92	0.0006	0.6223
V4-93	0.6952	0.6518
V4-94	0.0000	0.0000
V4-96	0.0000	0.2220
V4-98	0.0000	0.0072
V4-99	0.0000	0.6352
V4-100	0.0001	0.9909
V4-101	0.0034	0.6244
V4-106	0.0000	0.6773
V4-125	0.0000	0.0095

Table 2 | Significance of cue response
P values for Wilcoxon rank-sum tests performed on each channel muax responses between conditions.

Monkey H

	HH vs LL	HL vs LH
V4-1	0.0000	0.0000
V4-2	0.0000	0.0000
V4-3	0.0000	0.0000
V4-4	0.0000	0.0000
V4-5	0.0000	0.0000
V4-6	0.0000	0.0000
V4-7	0.0000	0.0000
V4-8	0.0000	0.0000
V4-9	0.0000	0.0000
V4-10	0.0000	0.0000
V4-11	0.0000	0.0000
V4-12	0.0000	0.0000
V4-13	0.0000	0.0000
V4-14	0.0000	0.0000
V4-15	0.0000	0.0000
V4-16	0.0000	0.0000
V4-17	0.0000	0.0000
V4-18	0.0000	0.0000
V4-19	0.0000	0.0000
V4-20	0.0000	0.0000
V4-21	0.0000	0.0000
V4-22	0.0000	0.0000
V4-23	0.0000	0.0000
V4-24	0.0000	0.0000
V4-25	0.0000	0.0000
V4-26	0.0000	0.0000
V4-27	0.0000	0.0000
V4-28	0.0000	0.0000
V4-29	0.0000	0.0000
V4-30	0.0000	0.0000
V4-31	0.0000	0.0000
V4-32	0.0000	0.0000
V4-33	0.0000	0.0000
V4-34	0.0970	0.0931
V4-35	0.0000	0.0000
V4-36	0.0000	0.0000
V4-37	0.0000	0.0000
V4-38	0.0000	0.0000
V4-39	0.0000	0.0000
V4-40	0.0000	0.0000
V4-41	0.0000	0.0000
V4-42	0.0000	0.0000
V4-43	0.0000	0.0000
V4-44	0.0000	0.0000
V4-45	0.0000	0.0000
V4-46	0.0000	0.0000
V4-47	0.0000	0.0000
V4-48	0.0000	0.0000
V4-49	0.0000	0.0000
V4-50	0.0000	0.0009
V4-51	0.0000	0.0000
V4-52	0.0000	0.0000
V4-53	0.0000	0.0000
V4-56	0.0006	0.0000
V4-57	0.0000	0.0000
V4-58	0.0000	0.0000
V4-59	0.0000	0.0000
V4-60	0.0000	0.0000

Monkey K

	HH vs LL	HL vs LH
V4-64	0.0001	0.0000
V4-65	0.0006	0.0003
V4-66	0.0001	0.0000
V4-67	0.0132	0.0000
V4-68	0.0023	0.0000
V4-69	0.4369	0.0222
V4-71	0.0035	0.0000
V4-72	0.6753	0.0136
V4-73	0.0331	0.0261
V4-74	0.3635	0.0000
V4-75	0.0042	0.0003
V4-76	0.3800	0.0000
V4-80	0.1858	0.0067
V4-81	0.4869	0.0001
V4-82	0.1775	0.0008
V4-83	0.0052	0.2764
V4-84	0.0331	0.0007
V4-85	0.0135	0.0335
V4-87	0.0007	0.0000
V4-88	0.7158	0.0039
V4-91	0.0585	0.0001
V4-92	0.4611	0.0026
V4-93	0.0746	0.0067
V4-94	0.1822	0.0385
V4-96	0.0860	0.0000
V4-98	0.0020	0.0001
V4-99	0.0748	0.0003
V4-100	0.1622	0.0015
V4-101	0.2362	0.0000
V4-106	0.0000	0.0190
V4-125	0.0011	0.0611

Table 3 | Significance of cue time
P values for Wilcoxon rank-sum tests performed on each channel muax responses between conditions.

Monkey H

	HH vs LL	HL vs LH
V4-1	0.0000	0.0000
V4-2	0.0000	0.0947
V4-3	0.0000	0.0018
V4-4	0.0000	0.0000
V4-5	0.0000	0.6140
V4-6	0.0000	0.0000
V4-7	0.0000	0.0000
V4-8	0.0000	0.0000
V4-9	0.0000	0.0000
V4-10	0.0000	0.0000
V4-11	0.0000	0.0099
V4-12	0.0000	0.0192
V4-13	0.0000	0.3403
V4-14	0.0000	0.0530
V4-15	0.0000	0.0000
V4-16	0.0000	0.0000
V4-17	0.0000	0.0042
V4-18	0.0000	0.0002
V4-19	0.0000	0.0000
V4-20	0.0000	0.0001
V4-21	0.0000	0.0000
V4-22	0.0000	0.8824
V4-23	0.0000	0.0001
V4-24	0.0000	0.0405
V4-25	0.0000	0.0000
V4-26	0.0000	0.0001
V4-27	0.0000	0.0319
V4-28	0.0000	0.0084
V4-29	0.0000	0.1310
V4-30	0.0000	0.0084
V4-31	0.0000	0.1052
V4-32	0.0000	0.0001
V4-33	0.0000	0.0000
V4-34	0.0000	0.0163
V4-35	0.0000	0.0000
V4-36	0.0000	0.0000
V4-37	0.0000	0.0000
V4-38	0.0000	0.0098
V4-39	0.0000	0.0174
V4-40	0.0000	0.0006
V4-41	0.0000	0.0039
V4-42	0.0000	0.1083
V4-43	0.0005	0.1689
V4-44	0.0000	0.0003
V4-45	0.0000	0.0000
V4-46	0.0000	0.0002
V4-47	0.0000	0.0295
V4-48	0.0000	0.0218
V4-49	0.0000	0.0000
V4-50	0.0000	0.0060
V4-51	0.0000	0.0322
V4-52	0.0000	0.0661
V4-53	0.0000	0.0168
V4-56	0.0000	0.0378
V4-57	0.0000	0.0006
V4-58	0.0003	0.0046
V4-59	0.0000	0.0037
V4-60	0.0000	0.0001

Monkey K

	HH vs LL	HL vs LH
V4-64	1.0000	0.9370
V4-65	0.8590	0.0011
V4-66	0.0691	0.0443
V4-67	0.6370	0.5605
V4-68	0.8854	0.0113
V4-69	0.8926	0.4521
V4-71	0.1832	0.0002
V4-72	0.9958	0.9997
V4-73	0.9759	0.2218
V4-74	0.8737	0.6499
V4-75	0.1113	0.1072
V4-76	0.8520	0.4776
V4-80	0.0144	0.9942
V4-81	0.7978	0.9746
V4-82	0.9990	0.5935
V4-83	0.9982	1.0000
V4-84	0.5702	0.7588
V4-85	0.9999	0.9802
V4-87	0.3418	0.2298
V4-88	0.6855	0.9949
V4-91	0.0763	0.9710
V4-92	0.2885	1.0000
V4-93	0.7174	0.8542
V4-94	0.7727	0.9849
V4-96	0.6009	0.9862
V4-98	0.7990	1.0000
V4-99	0.9951	1.0000
V4-100	0.0204	0.9998
V4-101	0.2149	0.5669
V4-106	0.7688	1.0000
V4-125	0.0001	0.9843

Table 4 | Significance of average post cue response
P values for Wilcoxon rank-sum tests performed on each channel muax responses between conditions.

Monkey H

	HH vs LL	HL vs LH
V4-1	0.0015	0.0699
V4-2	0.0002	0.0166
V4-3	0.4380	0.0324
V4-4	0.0031	0.0180
V4-5	0.0443	0.5655
V4-6	0.0003	0.1221
V4-7	0.0000	0.0492
V4-8	0.0001	0.2899
V4-9	0.0000	0.0017
V4-10	0.0000	0.0088
V4-11	0.0001	0.0733
V4-12	0.0001	0.0127
V4-13	0.1292	0.3421
V4-14	0.0091	0.6819
V4-15	0.0027	0.3984
V4-16	0.0007	0.4762
V4-17	0.0000	0.0859
V4-18	0.0007	0.1366
V4-19	0.0000	0.0209
V4-20	0.0027	0.5118
V4-21	0.0006	0.1552
V4-22	0.0019	0.7881
V4-23	0.0000	0.0491
V4-24	0.0780	0.4396
V4-25	0.0275	0.1793
V4-26	0.0036	0.1875
V4-27	0.1524	0.0660
V4-28	0.0090	0.0044
V4-29	0.0765	0.1534
V4-30	0.0004	0.0381
V4-31	0.0018	0.0353
V4-32	0.0000	0.0120
V4-33	0.0006	0.0047
V4-34	0.1520	0.0232
V4-35	0.0059	0.0057
V4-36	0.0000	0.4549
V4-37	0.0000	0.0995
V4-38	0.0792	0.6286
V4-39	0.0009	0.0660
V4-40	0.0000	0.4607
V4-41	0.0000	0.1104
V4-42	0.0001	0.0581
V4-43	0.0003	0.0002
V4-44	0.0012	0.0005
V4-45	0.0057	0.0016
V4-46	0.0013	0.0489
V4-47	0.0020	0.0048
V4-48	0.2728	0.0439
V4-49	0.0366	0.0509
V4-50	0.0006	0.0000
V4-51	0.0000	0.0242
V4-52	0.0017	0.3485
V4-53	0.0001	0.0198
V4-56	0.8003	0.0007
V4-57	0.0263	0.0369
V4-58	0.0001	0.0025
V4-59	0.0000	0.0088
V4-60	0.0000	0.3035

Monkey K

	HH vs LL	HL vs LH
V4-64	0.9302	0.2298
V4-65	0.0249	0.9182
V4-66	0.0002	0.0379
V4-67	0.0654	0.0000
V4-68	0.1393	0.3771
V4-69	0.7872	0.8261
V4-71	0.4381	0.0421
V4-72	0.0158	0.2506
V4-73	0.2040	0.1543
V4-74	0.1384	0.0453
V4-75	0.0198	0.0000
V4-76	0.0653	0.0000
V4-80	0.0706	0.4614
V4-81	0.0148	0.4063
V4-82	0.1726	0.0009
V4-83	0.0245	0.8186
V4-84	0.7273	0.0024
V4-85	0.7300	0.0001
V4-87	0.0035	0.0261
V4-88	0.0001	0.0625
V4-91	0.0055	0.0001
V4-92	0.0294	0.4278
V4-93	0.1514	0.1196
V4-94	0.0000	0.2736
V4-96	0.0065	0.9523
V4-98	0.0141	0.0012
V4-99	0.5645	0.3657
V4-100	0.1625	0.2555
V4-101	0.2531	0.0000
V4-106	0.0019	0.6996
V4-125	0.0218	0.0000

Table 5 | Significance of response to upwards motion
P values for Wilcoxon rank-sum tests performed on each channel muax responses between conditions.

Monkey H

	HH vs LL	HL vs LH
V4-1	0.0000	0.0170
V4-2	0.0000	0.0507
V4-3	0.0000	0.0027
V4-4	0.0000	0.0012
V4-5	0.0003	0.1727
V4-6	0.0000	0.0132
V4-7	0.0000	0.1041
V4-8	0.0000	0.0388
V4-9	0.0000	0.0003
V4-10	0.0000	0.8170
V4-11	0.0000	0.0493
V4-12	0.0000	0.0178
V4-13	0.0000	0.2998
V4-14	0.0000	0.6394
V4-15	0.0000	0.3687
V4-16	0.0000	0.0169
V4-17	0.0000	0.1174
V4-18	0.0000	0.0254
V4-19	0.0000	0.0138
V4-20	0.0000	0.0002
V4-21	0.0000	0.0017
V4-22	0.0000	0.0014
V4-23	0.0000	0.0515
V4-24	0.0000	0.0048
V4-25	0.0000	0.3529
V4-26	0.0001	0.2280
V4-27	0.0002	0.9055
V4-28	0.0049	0.2870
V4-29	0.0002	0.3332
V4-30	0.0029	0.3442
V4-31	0.0000	0.2685
V4-32	0.0000	0.0154
V4-33	0.0000	0.0025
V4-34	0.0192	0.2638
V4-35	0.0124	0.0878
V4-36	0.0000	0.7899
V4-37	0.0000	0.9011
V4-38	0.0003	0.9963
V4-39	0.0003	0.1503
V4-40	0.0010	0.7994
V4-41	0.0000	0.5243
V4-42	0.0454	0.0108
V4-43	0.0029	0.1850
V4-44	0.0000	0.2005
V4-45	0.0000	0.0227
V4-46	0.0000	0.0622
V4-47	0.0000	0.7504
V4-48	0.0000	0.0879
V4-49	0.0000	0.0143
V4-50	0.4406	0.9898
V4-51	0.0001	0.4291
V4-52	0.0001	0.2373
V4-53	0.0315	0.0103
V4-56	0.0086	0.4327
V4-57	0.0006	0.7739
V4-58	0.0035	0.2510
V4-59	0.0000	0.3120
V4-60	0.0005	0.0042

Monkey K

	HH vs LL	HL vs LH
V4-64	0.0154	0.0073
V4-65	0.2338	0.0041
V4-66	0.3916	0.0107
V4-67	0.2765	0.3561
V4-68	0.1754	0.3330
V4-69	0.0415	0.0000
V4-71	0.0039	0.2976
V4-72	0.0217	0.6247
V4-73	0.2587	0.0275
V4-74	0.4457	0.0322
V4-75	0.0000	0.0000
V4-76	0.2151	0.0248
V4-80	0.3899	0.9982
V4-81	0.1107	0.9647
V4-82	0.0118	0.1067
V4-83	0.0000	0.0247
V4-84	0.2664	0.0251
V4-85	0.0865	0.2403
V4-87	0.0007	0.0827
V4-88	0.0001	0.0260
V4-91	0.0431	0.0001
V4-92	0.1825	0.0198
V4-93	0.0832	0.0002
V4-94	0.0001	0.0715
V4-96	0.0405	0.8183
V4-98	0.0302	0.0016
V4-99	0.0760	0.7890
V4-100	0.0223	0.0152
V4-101	0.4133	0.0013
V4-106	0.0451	0.3391
V4-125	0.2537	0.0040

Table 6 | Significance of response to downwards motion
P values for Wilcoxon rank-sum tests performed on each channel muax responses between conditions.

Monkey H

	Up vs Down
V4-1	0.0004
V4-2	0.0000
V4-3	0.0017
V4-4	0.0025
V4-5	0.0000
V4-6	0.0000
V4-7	0.0025
V4-8	0.0000
V4-9	0.0000
V4-10	0.0000
V4-11	0.0004
V4-12	0.0000
V4-13	0.0000
V4-14	0.0000
V4-15	0.0002
V4-16	0.0521
V4-17	0.0000
V4-18	0.0000
V4-19	0.0000
V4-20	0.0000
V4-21	0.0000
V4-22	0.0000
V4-23	0.0000
V4-24	0.1416
V4-25	0.0000
V4-26	0.0000
V4-27	0.0042
V4-28	0.0000
V4-29	0.6344
V4-30	0.0000
V4-31	0.0000
V4-32	0.0000
V4-33	0.0000
V4-34	0.0000
V4-35	0.0000
V4-36	0.0111
V4-37	0.0000
V4-38	0.0000
V4-39	0.0000
V4-40	0.0000
V4-41	0.0000
V4-42	0.0000
V4-43	0.0000
V4-44	0.0000
V4-45	0.0157
V4-46	0.0000
V4-47	0.0000
V4-48	0.0000
V4-49	0.0001
V4-50	0.0000
V4-51	0.0000
V4-52	0.0000
V4-53	0.0000
V4-56	0.0000
V4-57	0.0010
V4-58	0.0000
V4-59	0.0000
V4-60	0.0000

Monkey K

	Up vs Down
V4-64	0.0000
V4-65	0.0000
V4-66	0.0005
V4-67	0.0000
V4-68	0.0262
V4-69	0.0436
V4-71	0.0000
V4-72	0.0000
V4-73	0.0006
V4-74	0.0000
V4-75	0.0000
V4-76	0.0000
V4-80	0.0038
V4-81	0.0000
V4-82	0.0000
V4-83	0.0000
V4-84	0.0000
V4-85	0.0343
V4-87	0.0000
V4-88	0.0000
V4-91	0.0000
V4-92	0.0000
V4-93	0.0000
V4-94	0.0027
V4-96	0.0005
V4-98	0.0000
V4-99	0.0040
V4-100	0.0000
V4-101	0.0062
V4-106	0.0002
V4-125	0.8531

Table 7 | Significance of motion selectivity
P values for Wilcoxon rank-sum tests performed on each channel muax responses between up and down motion.

Monkey H

	Equal	Unequal
V4-1	0.4175	0.5896
V4-2	0.0000	0.1628
V4-3	0.3264	0.5272
V4-4	0.2809	0.0787
V4-5	0.0168	0.0135
V4-6	0.0000	0.0542
V4-7	0.6903	0.0140
V4-8	0.0158	0.0000
V4-9	0.0162	0.5521
V4-10	0.0106	0.1948
V4-11	0.2103	0.2473
V4-12	0.0000	0.0000
V4-13	0.0000	0.0000
V4-14	0.0001	0.0018
V4-15	0.2559	0.0154
V4-16	0.9803	0.3948
V4-17	0.0000	0.0003
V4-18	0.0000	0.0124
V4-19	0.2948	0.8664
V4-20	0.0000	0.8406
V4-21	0.0000	0.0017
V4-22	0.0000	0.0001
V4-23	0.0001	0.0611
V4-24	0.9450	0.0758
V4-25	0.0000	0.0001
V4-26	0.0000	0.0000
V4-27	0.5010	0.0141
V4-28	0.0001	0.0001
V4-29	0.3987	0.8240
V4-30	0.0027	0.0182
V4-31	0.0023	0.2032
V4-32	0.0209	0.2360
V4-33	0.3141	0.5182
V4-34	0.0000	0.0000
V4-35	0.0000	0.0052
V4-36	0.7398	0.7728
V4-37	0.0202	0.0354
V4-38	0.6480	0.3748
V4-39	0.0000	0.0000
V4-40	0.0000	0.8211
V4-41	0.0448	0.0352
V4-42	0.7314	0.3909
V4-43	0.0000	0.0000
V4-44	0.0000	0.0367
V4-45	0.5893	0.0043
V4-46	0.0000	0.0618
V4-47	0.0000	0.0004
V4-48	0.0000	0.0000
V4-49	0.2125	0.0632
V4-50	0.0000	0.0000
V4-51	0.0763	0.2627
V4-52	0.0000	0.0000
V4-53	0.0000	0.7541
V4-56	0.0000	0.0000
V4-57	0.3155	0.4598
V4-58	0.0000	0.0000
V4-59	0.0000	0.0011
V4-60	0.0000	0.0090

Monkey K

	Equal	Unequal
V4-64	0.7918	0.8280
V4-65	0.2988	0.8483
V4-66	0.6383	0.9552
V4-67	0.0024	0.4100
V4-68	0.2158	0.2209
V4-69	0.0037	0.6617
V4-71	0.0000	0.0002
V4-72	0.1308	0.7583
V4-73	0.5697	0.7651
V4-74	0.0002	0.9902
V4-75	0.0000	0.0000
V4-76	0.0013	0.3765
V4-80	0.1559	0.2481
V4-81	0.3706	0.0493
V4-82	0.0001	0.0032
V4-83	0.0378	0.4775
V4-84	0.5781	0.1416
V4-85	0.2109	0.0297
V4-87	0.1758	0.4205
V4-88	0.3390	0.2703
V4-91	0.0004	0.2126
V4-92	0.5450	0.4804
V4-93	0.8297	0.6361
V4-94	0.0049	0.3928
V4-96	0.0008	0.7346
V4-98	0.0034	0.1238
V4-99	0.1465	0.7209
V4-100	0.0477	0.6118
V4-101	0.1457	0.6498
V4-106	0.9242	0.1822
V4-125	0.0997	0.3890

Table 8 | Significance of choice probabilites
P values for Wilcoxon rank-sum tests performed on choice probabilites for equal and unequal reward conditions.

Monkey H

	Sure vs Unsure
V4-1	0.8666
V4-2	0.7843
V4-3	0.1901
V4-4	0.9182
V4-5	0.5115
V4-6	0.1664
V4-7	0.5018
V4-8	0.0561
V4-9	0.6088
V4-10	0.5642
V4-11	0.1158
V4-12	0.7566
V4-13	0.6401
V4-14	0.5975
V4-15	0.2056
V4-16	0.0043
V4-17	0.9809
V4-18	0.6885
V4-19	0.9434
V4-20	0.7046
V4-21	0.1637
V4-22	0.3434
V4-23	0.8202
V4-24	0.0991
V4-25	0.5700
V4-26	0.8148
V4-27	0.7198
V4-28	0.9316
V4-29	0.1338
V4-30	0.2462
V4-31	0.2338
V4-32	0.9458
V4-33	0.5743
V4-34	0.0493
V4-35	0.8889
V4-36	0.6108
V4-37	0.0962
V4-38	0.0881
V4-39	0.9070
V4-40	0.0054
V4-41	0.5875
V4-42	0.0163
V4-43	0.0008
V4-44	0.9248
V4-45	0.4132
V4-46	0.0753
V4-47	0.0130
V4-48	0.3397
V4-49	0.0139
V4-50	0.0841
V4-51	0.7081
V4-52	0.8000
V4-53	0.0083
V4-56	0.5706
V4-57	0.4662
V4-58	0.1607
V4-59	0.5911
V4-60	0.1490

Monkey K

	Sure vs Unsure
V4-64	0.0278
V4-65	0.2132
V4-66	0.7812
V4-67	0.2258
V4-68	0.0272
V4-69	0.1838
V4-71	0.2392
V4-72	0.9252
V4-73	0.0754
V4-74	0.5495
V4-75	0.0687
V4-76	0.1235
V4-80	0.0026
V4-81	0.5259
V4-82	0.0021
V4-83	0.0205
V4-84	0.0346
V4-85	0.4710
V4-87	0.0402
V4-88	0.0128
V4-91	0.0728
V4-92	0.6421
V4-93	0.0270
V4-94	0.3002
V4-96	0.5641
V4-98	0.0100
V4-99	0.1181
V4-100	0.5069
V4-101	0.1071
V4-106	0.8040
V4-125	0.0040

Table 9 | Significance of certainty
P values for Wilcoxon rank-sum tests performed on each channel muax responses between sure and unsure.

Curriculum vitae

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Education

Current	**Radboud University**, Nijmegen Advisors: Prof. Dr. Pascal Fries and Dr. Michael Schmid
2012-2017	International Max Planck Research School **(IMPRS) for Neural Circuits**, Frankfurt Ernst Strüngmann Institute for Neuroscience GPA (German): 1.7/6
2004-2012	**The Open University**, UK 180 ECTS (Physics, Psychology, Mathematics, Biology)
Aug. 2011	BSc (Hons) Neuroscience, **University College London**, London Thesis: "A behavioural task to allow the manipulation of oscillations in the visual cortex of awake mice" | Advisor: Dr. Michael Häusser Result: 2.1 (68.75%)

Research Positions

Current May 2017	**Neuroscience Researcher** Frankfurt Institute for Advanced Studies and Ernst Strüngmann Institute for Neuroscience Singer Emeritus group of *Wolf Singer* Theoretical neuroscientist investigating high dimensional state space of the visual cortex.
Sept. 2012- April 2017	**Neuroscience PhD student** Ernst Strüngmann Institute for Neuroscience Visual Perception Lab of *Michael Schmid* Experimental neuroscientist investigating visual cortex and thalamic regions Experience of both recording and data analysis of large multichannel datasets, neurophysiological recordings from both awake and anesthetized macaques, designing psychophysical tasks for human and macaque subjects.
June 2010- Sept. 2011	**Research Assistant** Wolfson Institute of Biomedical Sciences, London Neural Computation Lab of *Michael Häusser* Received a stipend to set up a virtual reality system for mice programming the virtual reality environment and animal training. This was extended to the use of optogenetic techniques to manipulate the visual cortex of mice during task performance. Other tasks included improving staining techniques and beginning multi-electrode recordings during awake behaviour.

Scientific Papers

2017	Kurtz, P., **Shapcott, K. A.**, Kaiser, J., Schmiedt, J. T., Schmid, M. C. The Influence of Endogenous and Exogenous Spatial Attention on Decision Confidence. Submitted
	Kienitz, R., Schmiedt, J. T., **Shapcott, K. A.**, Kouroupaki, K., Saunders R. C., Schmid, M. C. Rhythmic spiking and attentional sampling arise from cortical receptive field interactions. In preparation
2016	**Shapcott, K. A.**, Schmiedt, J. T., Saunders, R. C., Maier, A., Leopold, D. A., & Schmid, M. C. (2016). Correlated activity of cortical neurons survives extensive removal of feedforward sensory input. Scientific Reports, 6:34886.
	Klein, C., Evrard, H. C., **Shapcott, K. A.**, Haverkamp, S., Logothetis, N. K., & Schmid, M. C. (2016). Cell-targeted optogenetics and electrical microstimulation reveal the primate koniocellular projection to supra-granular visual cortex. Neuron, 90(1), 143-151.

Conference Abstracts

2016	**Shapcott, K. A.**, Kienitz, R., Kouroupaki, K., Schmiedt, J. T., & Schmid, M. C. (2016). Reward related suppression in visual area V4 during a discrimination task. Symposium on Biology of Decision Making
	Kurtz, P., **Shapcott, K. A.**, & Schmid M. C. (2016). Task to investigate the effects of exogenous and endogenous spatial attention on perceptual confidence. Symposium on Biology of Decision Making
	Kienitz, R., Schmiedt, J. T., **Shapcott, K. A.**, Kouroupaki, K., Schmid, M. C. Theta-rhythmic spiking of visual cortical area V4 neurons arises from receptive field center-surround interactions. 800.09. Annual Meeting of the Society for Neuroscience
	Peter, A., Dowdall, J., Klein, L., Klon-Lipok, J., Kouroupaki, K., Schmiedt, J. T., **Shapcott, K. A.**, Schmid, M. C., Singer, W., Fries, P. Gamma-band synchronization in primate visual cortex can increase or decrease with stimulus repetition. 242.05. Annual Meeting of the Society for Neuroscience

Workshops and Talks

Nov. 2016	Data Science and Data Skills for Neuroscientists
July 2016	ESISync Circuit Computation
April 2016	IMPRS for Neural Circuits Retreat- Selected Speaker
	Title: "Visual Area V4: Noise Correlations Without V1 and Reward Related Activity."
2015	ESISync Brain Codes
2014	ESI Systems Neuroscience Conference
2013	Alpha: from mechanism to cognition
	Neuronal Recordings and Stimulation
	FELASA B course
2010	UK Home Office accredited animal licensee training course

Languages

English: Native
German: Conversational
French: Conversational